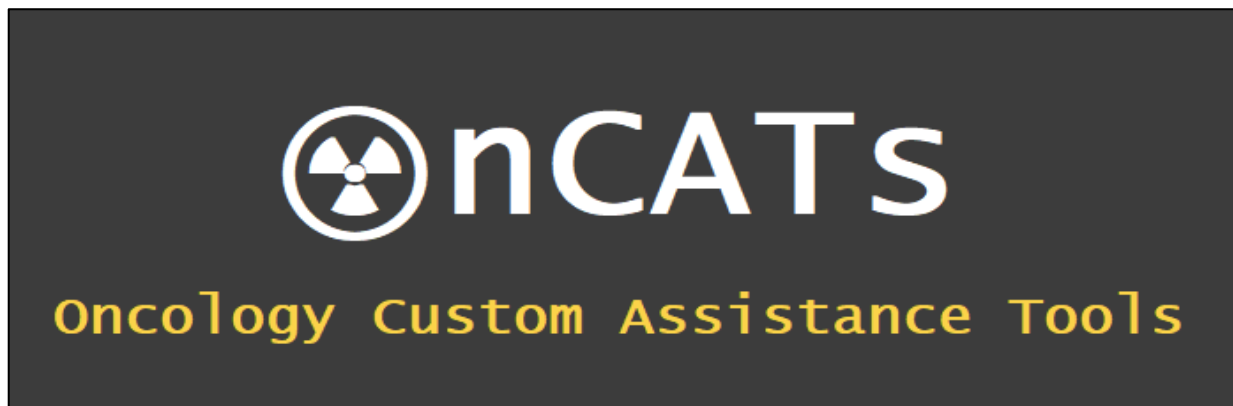


Polytechnic Institute of Lisbon

Lisbon Superior Engineering Institute

Lisbon School of Health Technology



Thesis to obtain the Master of Science (MSc) degree in
Biomedical Engineering

Development of a Decision Support System in Oncology for Prostate Adenocarcinoma

(Definitive Version)

João Pedro Leite Silva Costa

Supervisors:

Professor Doutor Nuno Domingues, Instituto Superior de Engenharia de Lisboa

Professor Filipe Moura, Escola Superior de Tecnologia da Saúde de Lisboa

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Abstract

Healthcare professionals are constantly faced with new developments on the medical practice. In Oncology, diseases have high heterogeneity, and a greater need of providing individual healthcare measures exists, since every patient displays different characteristics, medical histories and lifestyles. Individualized medical practices are a constant process of decision-making, with several possible courses of action. Since choosing the best available option can maximize the success of treatment and minimize the harm done to the patient, a greater need emerges for healthcare professionals to be vigilant of all developments in the medical research. The goal of this study is to develop a knowledge based clinical Decision Support System (DSS) for assessment and treatment in Oncology, named Oncology Custom Assistance Tools (OnCATs). A clinical DSS is a computerized system designed to assist a healthcare professional on performing a very high-demanding task that involves making one or more decisions, while saving time and reducing errors. The ultimate focus the project is to evaluate if OnCATs can precisely characterize a patient into a definitive risk group, assess all the available treatment options and individually prescribe every treatment that is part of the chosen treatment course.

It was understood that OnCATs can accurately simulate the clinical workflow for treatment of localized prostate cancers patients, providing clear evidence-based information, useful for any kind of task in the oncology workflow of treatment. The system also constitutes a method for a healthcare professional to assess all treatment variable options, in a short period of time, before making a definitive decision, which allows saving time and resources, optimizing the overall flow of work. The system's output is based on a universal well-understood medical language, easy to comprehend and report by all healthcare professionals.

The development of this algorithm proved to be an efficient way to computerize a medical process, and make it assessible to healthcare professionals, by the means of an easy-to-use digital tool. Prostate cancer was shown to be an adequate starting point for the development of the system, due to providing a solid learning curve, all the steps necessary to expand this method to other kinds of diseases are now well established, showing great promise on its future applications.

Keywords: Prostate cancer, Clinical decision support system, Radiotherapy, Radical prostatectomy, Androgen Deprivation Therapy (ADT).

Resumo

Nos dias que correm, os profissionais de saúde são constantemente confrontados com novos desenvolvimentos nas práticas médicas. Em Oncologia, está presente uma grande heterogeneidade nas mais diferentes patologias, e assim, surge uma maior necessidade de fornecer cuidados médicos individualizados, uma vez que cada doente exhibe diferentes características, históricos médicos e estilos de vidas. Cuidados médicos individualizados são um processo constante de tomada de decisões, devido às várias características e abordagens terapêuticas diferentes que se têm de ter em conta. Uma vez que a escolha da melhor opção de tratamento disponível pode altamente maximizar o sucesso de tratamento e minimizar os efeitos secundários sofridos pelo doente, surge uma maior necessidade para os profissionais de saúde estarem vigilantes e ocorrentes de todos os desenvolvimentos consequentes da investigação médica.

O objetivo deste estudo é desenvolver um Sistema de Suporte à Decisão clínica para gestão e tratamento em Oncologia, nomeado de Oncology Custom Assistance Tools (OnCATs). Um Sistema de Suporte à Decisão clínica é uma ferramenta computadorizada que tem o intuito de auxiliar os profissionais de saúde a desempenhar tarefas altamente exigentes, que requerem a tomada constante de decisões, permitindo ao mesmo tempo poupar o tempo despendido na realização dessas tarefas e reduzir os erros. O principal foco deste projeto é avaliar se o OnCATs é capaz de caracterizar precisamente um doente num determinado grupo de risco, avaliar quais as opções terapêuticas mais indicadas para esse doente, e prescrever individualmente cada modalidade tratamento que faz parte de uma abordagem terapêutica multimodalidade. O algoritmo do sistema será validado recorrendo a casos clínicos, comparando os resultados obtidos para cada caso clínico com a abordagem que foi clinicamente aplicada.

O desenvolvimento deste estudo pode ser dividido em três fases. A primeira fase foi constituída pela obtenção de uma vasta quantidade de informação médica que permitisse a construção de uma base de dados, relativa às práticas atuais em oncologia e gestão do doente. Na segunda fase, a interface do sistema foi informaticamente construída, de forma a integrar digitalmente a base de dados obtida e a permitir a comunicação do utilizador do com a mesma e, por consequência, a exportação de resultados sobre a forma de um relatório médico. Na última fase, os casos clínicos obtidos recorrendo à literatura, foram então submetidos ao algoritmo do OnCATs de modo a testar o fluxo de funcionamento do sistema e verificar as suas condições de aplicabilidade.

Em termos de funcionamento, o fluxo de trabalho do sistema consiste em atribuir um grupo de risco, utilizando a nomenclatura do National Comprehensive Cancer Network (NCCN), com base no estadiamento, *Score* de Gleason (GS) e concentração do antígeno específico da próstata (PSA). Seguidamente, com base no grupo de risco, esperança média de vida, presença de sintomas e características adversas da doença, o sistema será capaz de recomendar uma, e se possível mais que uma, abordagem terapêutica para esse determinado doente, incluindo Observação (*Observation*), Vigilância Ativa (*Active Surveillance*), Radioterapia Externa, Braquiterapia, Cirurgia, Hormonoterapia (*Androgen Deprivation Therapy*), e 10 outros regimes terapêuticos constituídos por diferentes combinações das diferentes terapêuticas isoladas acima mencionadas. Após a decisão da abordagem terapêutica por parte do utilizador, o sistema é capaz de auxiliar a prescrição individual e combinada de cada um desses 14 diferentes cursos de tratamento.

Assim, verificou-se que o OnCATs é capaz de sintetizar precisamente o fluxo de trabalho clínico empregado ao tratamento dos doentes com cancro da próstata localizado, fornecendo informação clara e baseada em evidência clínica, útil para qualquer tipo de tarefa a desempenhar nas práticas atuais em oncologia. Para além disso, o sistema constitui um método eficiente para os profissionais de saúde verificarem, num curto intervalo de tempo, quais as opções terapêuticas disponíveis para tratar um determinado doente, antes da tomada de qualquer decisão definitiva, permitindo assim a poupança de tempo e recursos. O *output* gerado pelo sistema é baseado numa nomenclatura médica empregue universalmente e bem estabelecida, o que permite a sua fácil compreensão e a estimula a passagem clara de informação entre profissionais de saúde.

O desenvolvimento deste algoritmo provou ser um método eficiente para computadorizar um processo médico, tornando-o acessível a qualquer profissional de saúde, através de uma ferramenta digital fácil de utilizar. O cancro da próstata mostrou ser um ponto de partida adequado para o desenvolvimento do OnCATs. Devido a fornecer uma curva de aprendizagem sólida, permitiu ainda a ampla identificação de todos os passos necessários para expandir este método a outros tipos de doenças, demonstrando uma grande promessa em aplicações futuras.

A amostra de doentes utilizada para testar o sistema possui uma idade média de $69,7 \pm 5,9$ anos (59 – 77 anos) e uma esperança média de vida de $6,7 \pm 3,4$ anos (2,8 – 11,7 anos). 4 de 10 doentes (40 %) possuem um tumor com estadio T4 N0 M0, 3 doentes (30 %) possuem um tumor com estadio T2b N0 M0, e os restantes 3 doentes (30 %) possuem um tumor com estadio T1c N0 M0.

Relativamente aos grupos de risco, 1 doente (10 %) foi caracterizado como tendo uma doença de risco muito baixo, 3 doentes (30 %) foram caracterizados como tendo uma doença de risco intermédio, 2 doentes (20 %) foram caracterizados como tendo uma doença de alto risco e os restantes 4 doentes (40 %) foram caracterizados como tendo uma doença de risco muito alto. Quanto à avaliação da *performance* na avaliação dos regimes terapêuticos recomendáveis, foi observado que o sistema foi capaz de sugerir a opção terapêutica aplicada em 40 % dos casos. Nos restantes 60 %, o sistema sugeriu opções terapêuticas diferentes daquela que foi aplicada ao doente. O número médio de sugestões de curso de tratamento dadas pelo sistema para todos os casos clínicos foi $4,4 \pm 1,6$.

Quanto à análise da *performance* do sistema na prescrição de tratamentos de Radioterapia Externa, em 15 das 20 tarefas (75 %) o sistema apresentou como opção a abordagem aplicada ao doente. Quanto à prescrição de Hormonoterapia, em 14 das 21 tarefas (66,67 %) sistema apresentou como opção a abordagem aplicada ao doente.

De um modo geral, o OnCATs desempenhou com sucesso 45 das 56 tarefas (80,4 %) que constituíam todo o percurso de tratamento de todos os casos clínicos.

Individualmente, cada caso clínico teve uma taxa média de sucesso de $78,7 \% \pm 15,6 \%$.

Independentemente dos resultados obtidos após a submissão dos casos clínicos ao algoritmo do OnCATs, é relevante mencionar que é possível que diferentes médicos escolham diferentes abordagens terapêuticas, com base na sua própria lógica e experiência, sem comprometer os resultados e qualidade de vida dos doentes.

Futuramente, o próximo passo de desenvolvimento do OnCATs será criar medidas para que o sistema seja capaz de atualizar automaticamente a base de dados já existente, através de uma metodologia prática de *scanning* de documentos e armazenamento nessa mesma base de dados, recorrendo a tecnologias de inteligência artificial e *machine learning*.

Estas novas implementações poderão originar a identificação de novas variáveis relevantes para os resultados apresentados pelo sistema. A utilização de *big data* é um procedimento *standard* para as tecnologias em saúde, devido a permitir a previsão de resultados em escalas de maior dimensão. Como próximo objetivo de melhoria, a extensão do sistema a outros tipos de doença, nomeadamente cancro da próstata não-localizado, cancro da próstata com histologia diferente de adenocarcinoma, e outros tipos de cancro como cancro da mama ou cancro do reto, constituiu um grande benefício.

Palavras-chave: Cancro da próstata, Sistema de suporte à decisão clínica, Radioterapia, Prostatectomia radical, Hormonoterapia.

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List of acronyms and abbreviations

3DCRT - 3D-Conformal Radiotherapy	ESUR - European Society of Urogenital Radiology
AAPM - American Association of Physicists in Medicine	GTV – Gross Tumor Volume
ABS - American Brachytherapy Society	HDR – High-Dose Rate
ACR - American College of Radiology	HU – Hounsfield Units
ADT – Androgen Deprivation Therapy	IDE - Integrated Development Environment
AJCC - American Joint Committee on Cancer	IGRT – Image Guided Radiotherapy
AS – Active Surveillance	IMRT – Intensity Modulated Radiotherapy
ASCO - American Society of Clinical Oncology	ISUP - International Society of Urological Pathology
ASTRO - American Society for Radiation Oncology	IUCC - International Union for Cancer Control
AUA - American Urological Association	LDR – Low-Dose Rate
Cancer Care Ontario (CCO)	LH - Luteinizing Hormone
BT – Brachytherapy	LHRH - Luteinizing Hormone-Releasing Hormone
CC – Clinical Case	Linac - Linear Accelerator
CT – Computed Tomography	LQM – Linear Quadratic Model
CTV – Clinical Target Volume	mpMRI – Multi-parametric Magnetic Resonance Imaging
DCE MRI – Dynamic Contrast-Enhanced Magnetic Resonance Imaging	MRI - Magnetic Resonance Imaging
DNA - Deoxyribonucleic Acid	NCCEC - Nacional Clinical Effectiveness Committee
DRE – Digital Rectal Exam	NCCN - National Comprehensive Cancer Network
DSS – Decision Support System	NHS - National Health Service
DW MRI – Diffusion-Weighted Magnetic Resonance Imaging	NICE - National Institute for Health and Care Excellence
EAU - European Association of Urology	NTCP - Normal Tissue Complication Probability
EBRT – External Beam Radiotherapy	OAR – Organs At Risk
EORTC - European Organization for Research and Treatment of Cancer	OnCATs – Oncology Custom Assistance Tools
ESMO - European Society for Medical Oncology	PLND - Pelvic Lymph Node Dissection
ESTRO - European Society of Radiotherapy	

PSA – Prostate Specific Antigen
PTV – Planning Target Volume
RANZCR - Royal Australia and New Zealand College of Radiologists
RF – Radiofrequency
ROI – Region Of Interest
RP – Radical Prostatectomy
RSS - Radiosurgery Society
RT – Radiotherapy
SBRT – Stereotactic Body Radiotherapy
SIOG - International Society of Geriatric Oncology
SSA – Social Security Administration
SUO - Society of Urological Oncology
SVI – Seminal Vesicles Invasion
TCP - Tumor Control Probability
TE – Time of Echo
TNM – Tumor Node Metastasis
TPS – Treatment Planning System
TR – Repetition Time
TRUS – Trans-rectal Ultrasound
TURP – Transurethral Resection of the Prostate
US – Ultrasound
USA – United States of America
VB – Visual Basic
VMAT – Volumetric Modulated Arc Therapy
WHO – World Health Organization

List of symbols

α - Alpha
 β - Beta
GHz – Gigahertz
Gy – Gray
H₂O⁺ – Water Ion
J – Joule
kg - Kilogram
kV - Kilovolt
ml - milliliters
MV – Mega Volt
ng – nanograms
O₂⁻ - Superoxide
OH[•] - Hydroxyl

1. Introduction

Healthcare professionals are constantly faced with new research and discoveries on the medical field and practice. This overload of information is very hard to keep up with, as information is spread and becomes more and more easily accessible.¹ In Oncology, given the high heterogeneity among different diseases, a greater need of providing individual healthcare measures exists, in order to be able to achieve optimal results. Besides the heterogeneity among cancerous diseases, every patient displays different characteristics, medical histories and lifestyles. Individualized medical practices are a constant process of decision-making, as the path followed by a patient diagnosed with cancer has many different stages, with several possible courses of action. Since choosing the best available option can maximize the success of treatment and minimize the harm done to the patient, either by limiting disease progression or treatment side effects, a greater need emerges for healthcare professionals to be vigilant of all possible options and all new advances that are constantly happening in consequence of medical research.^{2,3}

A Decision Support System (DSS) is a computerized system designed to assist a competent user on performing a determined task that involves making one or more decisions. If this system is developed in order to be used on a medical task or workflow, it is often called a Clinical DSS. Clinical DSSs have been globally used with the aim of assisting healthcare professionals on very high-demanding daily tasks, while saving time and reducing medical errors.⁴ These systems combine the instructions given to a software by a healthcare professionals and simulate their logic and judgement, using knowledge of medical domain, represented by standard practices and workflows, achieving then a multi-factorial decision making assistance process.³

Regarding medical applications, the prostate is a gland with an approximate size of walnut, located beneath the bladder in human males. It contributes to the urinary flows and produces enzymes and components of semen. Since most of the prostatic tissue is glandular, the majority of prostate tumors are histologically adenocarcinomas, which is the terminology applied to tumors originated on glandular tissue. However, other histological types of prostate cancer, such as cribriform carcinomas, acinar-cell carcinomas and myosarcomas may still occur less frequently.⁵

In 2016, around 27% of all the deaths in Portugal were caused by malignant tumors, and this percentage has been constantly increasing since 1960. It is valued that 4000 new cases arise every year, being considered the second most frequent cause of death by cancer in the male population. Overall, prostate cancer represents 12% of all cancers in Europe.^{6,7}

Prostate cancer can be treated with several treatment options, such as External Beam Radiotherapy (EBRT), Brachytherapy (BT) or Radical Prostatectomy (RP). Choosing a treatment heavily depends not only on the patient's characteristics and physician's experience, but also on both their preferences. Besides that, the variety of treatments produce different side effects, which can cause a great impact on the patient's quality of life, satisfaction and treatment outcome.⁸ All these factors constitute optimal reasons for the implementation of a clinical DSS for assessment and treatment of prostate cancer. A clinical DSS can also be a valuable tool to improve early disease detection and reduce overtreatment and unnecessary examining of the patient. The development of these kind of tools is also necessary to efficiently compare the predicted outcomes of different treatment courses for a specific patient, which plays a great part on the process of deciding a treatment option for a patient.⁸

The goal of this study is to develop a knowledge based clinical DSS for assessment and treatment in Oncology. The developed clinical DDS was named Oncology Custom Assistance Tools (OnCATs). This name was chosen due to being descriptive of the application of the system, remoting to a computerized software which goal is to be used as an assistance tool for an oncology assistance application. The ultimate focus of this research project is to evaluate if OnCATs can be successfully applied to assist healthcare professionals in making decisions regarding medical tasks, namely those who are part of the workflow of treatment for an oncologic patient. Practically, this translates to OnCATs being able to successfully characterize a patient into a definitive risk group, to assess the available treatment options and to individually prescribe every treatment that is part of the chosen treatment course. The results should be exported in the form of a text report, elaborated in a comprehensive language to all healthcare professionals. The system will then be tested using relevant clinical cases available on literature, which were treated with different treatment courses and have different contexts. It is expected that the workflow of OnCATs can be validated by applying its algorithm to these clinical cases and comparing the results obtained for each case with their actual course of action.

As previously mentioned, prostate cancer has several available treatment options with expected results well reported. Having more options available makes the task more demanding in terms of decision-making, since there are more variables that have to be considered. Because of that, prostate cancer was chosen as the starting point for the development of OnCATs. Due to tumor histology playing an important role on choosing a treatment course, and metastatic disease treatment greatly vary with the location and number of metastasis, OnCATs first application was restricted to localized adenocarcinomas of the prostate.

2. State of the art and theoretical concepts

2.1 Risk assessment

Risk assessment, also referred to as risk stratification, is a predictive model that can be defined as the probability of a given cancer, such as prostate cancer, being confined to its place, organ, or tissue of origin, or being spread to the regional lymph nodes or distant areas. It also evaluates the probability of a tumor to metastasize after treatment and the probability of success after salvage treatment without biochemical recurrence. Sorting a patient into a determined risk group, is the starting point of the treatment workflow in oncology.^{9,10,19,20,11–18}

The use of this model is crucial for assessment of the optimal treatment course for a specific patient. The definition of risk groups is based on evidence and clinical research performed on large scales of patients grouped in clusters of patients with similar features and diseases.^{9,10,19,20,11–18} Categorizing patients into a risk group is an efficient and easy-to-use method to sort out which treatment courses are available and might be the most indicated to a given patient.²⁰ In the research and literature, most authors use the National Comprehensive Cancer Network® (NCCN) Guidelines for Prostate Cancer terminology, which is based on the system proposed by D'Amico et al. in 1998.^{9,21} Following the NCCN® Guidelines for Prostate Cancer terminology, it is possible to stratify prostate cancer patients into seven different risk groups⁹:

- Very low risk;
- Low risk;
- Intermediate risk;
- High risk;
- Very high risk;
- Regional disease;
- Metastatic disease.

These different risk groups can serve many purposes. They can assist in decision-making, characterize patients into distinct groups for clinical trials, and provide a mean of communication between healthcare professionals and institutions, by the use a common nomenclature.²⁰ Having this distinction, serves also as a baseline for physicians to explore possible treatment courses for a patient, for both multi-modality and single-modality treatments, knowing what to predict in terms of disease regression and toxicity. Besides that, it can also assist physicians to avoid overtreatment in selected cases where less invasive or palliative approaches are more indicated given the clinical condition of the patient.^{9,10,19,20,11–18}

Regardless of the used terminology, these three variables are always taken into account to categorize a patient into a risk group, due to being crucial prognostic factors for prostate tumors:^{9,10,19,20,11–18}

- Tumor stage;
- Gleason Score (GS);
- Prostate-specific antigen (PSA) serum concentration.

2.1.1 Tumor staging

Disease staging is defined as assessing in which state of progression a determined disease is. Staging a tumor allows us, to some extent, to predict a patient's outcome and prognosis, based on the results of clinical trials performed on groups of patients with diseases in similar stages. It also allows us to find similarities between patients, in order to characterize populations and assume conclusions from data obtained in clinical trials, allowing the comparison and discussion of the results with other studies.²²

Worldwide, the most common system in use is the Tumor Node Metastasis (TNM) system, developed by the American Joint Committee on Cancer (AJCC) in cooperation with the International Union for Cancer Control (IUCC). This system is revised every 6 – 8 years in order to always be up to date and relevant to the current medical practices and technology, and that is why it has stayed globally present on clinical practice throughout the years.²² This method consists on the analysis of these three variables:

- T, which stands for Tumor and characterizes tumor size, location and extension. It can assume values from 1 to 4, assuming grade 1 to be the best prognostic possible and grade 4 to be the worst prognostic possible;²²
- N, which stands for Nodes and characterizes the presence of metastasis located on the regional lymph nodes. It varies from 0 to 1, assuming that grade 0 is the absence of regional lymph node metastasis and grade 1 is the presence of regional lymph node metastasis;²²
- M, which stands for Metastasis and characterizes the presence of distant and/or non-regional lymphatic metastasis. It varies from 0 to 1, assuming that grade 0 is the absence of distant or non-regional lymphatic metastasis and grade 1 is the presence of distant and/or non-regional lymphatic metastasis.²²

The criteria used to assign a value to any of these variables depends from disease site, tumor location and histology, so specific guidelines do exist in order to assist physicians to characterize a tumor using the TNM grading system. The criteria used for staging prostate adenocarcinomas, using the TNM system, can be consulted on appendix 1.^{9,22}

2.1.2 Gleason score

The GS is a grading system for prostate cancer, developed by Gleason *et al.*, that has been widely used since 1966. This system was created out of the necessity to characterize the heterogeneity of adenocarcinomas of the prostate gland, since most tumors generally display two or more patterns on a cellular level. Since then, it has been endorsed by international entities like the World Health Organization (WHO), AJCC, IUCR and NCCN. Using the results of the histological analysis of a prostate tumor biopsy, this method uses the primary and secondary most extensive patterns visualized on the sample to characterize the tumor's heterogeneity.^{20,23}

A smaller sample of cells is taken from the largest visible differentiated area of the tissue sample, then, another small sample is taken from the second largest visible differentiated area of the sample. Both of these smaller samples are then individually graded after a microscopical analysis. To each pattern can be assigned a value ranging from 1 to 5. The sum of each grade is used to obtain the final grade, which can by consequence vary from 2 to 10. When only one major differentiated pattern is present, its grade is doubled to obtain the final GS.^{13,23} The interpretation of the final grade is done by comparing the collected samples with a normal and healthy prostatic glandular tissue pattern. By these means, this grading system can in fact predict the aggressiveness of a tumor located on prostatic tissue.²²⁻²⁵ Different GSs have different meanings:

- A total score inferior to 7 means that were only found individual discrete well-formed glands on both samples. This usually translates to a non-aggressive tumor with slow growing rates.^{9,20,22,24,25}
- A total score equal to 7 can have two different meanings. If the first pattern displays a value of 3 and the second a value of 4, it means that were found predominantly well-formed glands on the first sample, and lesser component of poorly formed, fused or cribriform glands on the second sample. This usually translates to non-aggressive tumors with good prognostic. If the first pattern displays a value of 4 and the second a value of 3, it means that predominantly poorly formed, fused or cribriform glands were found on the first sample, and lesser component of well-formed glands were found on the second sample. These tumors are considered aggressive, since they are more likely to grow and spread to other organs.^{9,20,22,25}
- A total score of 8 can also have different meanings. If both patterns display a value of 4, it means that only poorly formed, fused or cribriform glands were found on both samples. If the first pattern displays a value of 3 and the second a value of 5, it means that predominantly well-formed glands were found on the first sample, and lesser

component lacking glands such as, poorly formed, fused or cribriform glands, were found on the second sample. If the first pattern displays a value of 5 and the second a value of 3, it means that predominantly lacking glands were found on the first sample, and lesser component of well-formed glands, such as poorly formed, fused or cribriform glands, were found on the second sample. These tumors are highly differentiated and are more likely to spread.⁹

- A total score above 8, means that gland formation, or with necrosis, with or without poorly formed, fused or cribriform glands were formed on both samples. These are the most aggressive kind of prostate cancer, which usually grow and spread at fast rates.^{9,20,22,24,25}

Further explanation and a visual representation of the cellular patterns of the GS grades can be consulted on annex 1.²³

2.1.3 Prostate-specific antigen

PSA is an enzyme produced by the prostate gland, which is usually found in a concentration above normal range on patients with prostate cancer. This enzyme is used as serum tumor marker for adenocarcinomas of the prostate gland, due to that association between concentration on serum and the probability of presence of a malignant tumor on the prostate gland.^{20,26,27}

A PSA test consists on simply taking a blood sample from the patient and measuring the concentration of the PSA enzyme on the serum of that sample. When this value is abnormal and/or high, it may serve as an indication of the presence of an anomaly on the prostate gland, such as benign prostate hyperplasia, prostatitis or even a malign tumor.²⁶ Although there is not a certain value that predicts the presence of a tumor, it is widely assumed that an average of 15% of men with a PSA value inferior to 4 ng/ml have prostate cancer, 25% of men with a PSA value between 4 to 10 ng/ml have prostate cancer, and 50% of men with a PSA value greater than 10 ng/ml have prostate cancer.²⁶

Regardless of the test's value, additional means of assessment should be considered, since abnormalities other malignant tumors can cause variations on the PSA levels. Because of that, the result of a PSA test is not enough to make a diagnosis by itself, it should instead be used as an indication to evaluate if further testing should be considered or not.

2.2 Treatment assessment

After assigning a risk group to the patient, it is important to evaluate other characteristics not contemplated by the TNM staging, GS and PSA values. Characteristics such as patient symptoms, the presence of adverse feature, and the estimated life expectancy, are variables that are more closely related to each individual patient, which are especially important to differentiate patients that were assigned to the same risk group but that will not benefit from the same treatment course. Besides that, the evaluation of these characteristics, which should be ideally performed by a physician or by a multi-disciplinary team, is the key to provide an individualized healthcare approach, rather than simply following treatment protocols.⁹

Symptoms in medical oncology are the physical manifestations of a malignant tumor. Prostate cancer is often asymptomatic, and the symptoms tend to only manifest when the disease is in a higher stage. Since most of the symptoms are related and proportional to the size of the tumor, they tend to only show when the urethra is being physically pressed by the tumor, which is considered a sign of poor prognosis. Symptoms for prostate cancer include dysuria, nocturia, hematuria, urinary hesitancy, urinary retention, urinary incontinence and hematospermia, among others. Patients who manifest symptoms, need more urgent care in order to alleviate these symptoms and preserve quality of life as much as possible.²⁸

The adverse features of a tumor are characteristics of the tumor, that in the generality of cases, are indications of poor prognosis. They serve as an indication if a more aggressive variant of treatment should be employed or not. Generally, diseases who manifest at least one of these features, exhibit more aggressive traits and tend to progress faster. The principal adverse features consist on the following:⁹

- Positive margins;
- Seminal Vesicle Invasion (SVI);
- Extracapsular extension;
- Detectable PSA.

The concept of positive margins is only applied to a context where a previous surgical approach of treatment was conducted. The main goal of a surgical treatment is to resect the whole tumor, so the patient is declared free of disease. During the surgical procedure, the tumor is removed with a surgical margin defined around its borders, which serves as a measure of safety to decrease the probability of non-visible cancer cells, located around the tumor, being left on the patient's body. After the surgery, if some cancerous cells can still be found on the specimen's surgical margins, the patient is not declared cancer free and the disease is labeled as having positive margins, and a more aggressive treatment approach should be considered.²⁹

The seminal vesicles are a pair of accessory sex glands located above the prostate gland, which act as an anatomical storage site for semen. When SVI is present, it means that the disease has a higher probability of spreading to nearby healthy tissues and, therefore, more aggressive treatment approaches should therefore be considered.³⁰ On the other hand, extracapsular extension is defined as when the tumor grows or spreads beyond the fibromuscular capsule that surrounds the prostate gland, to a local place different than the seminal vesicles, such as the external sphincter or the pelvic wall.^{9,12,22} This factor is also marked as an indications of poor prognosis, as aggressive tumors tend to spread and grow faster. Both SVI and extracapsular extension can be assessed after a pathologic staging performed on a surgery specimen, or by precise means of imaging, such as Multi-parametric Magnetic Resonance Imaging (mpMRI) and ultra-sound (US) guided biopsy.^{30,31} Besides playing an important role on a choosing treatment approach, these factors are also important for defining surgical margins and margins for Radiotherapy (RT) treatments.^{9,12,22,30,31}

An estimation of the patient life expectancy is mandatory for treatment assessment, since aggressive approaches, such as surgery, would ideally only be applied to patients who have a relevant risk of dying from prostate cancer, and not from comorbidities. Because of that, it can make the difference between choosing a less invasive approach over a more aggressive approach.^{9,32} One way of estimating a patient life expectancy is using the Social Security Administration (SSA) life tables or the WHO life tables by country.^{9,32-34} These tables have as base the mortality expectancy of a population over a short period of time and provide an estimative of a person's life expectancy in years.^{9,32} This value can then be adjusted by the physician's judgement after observing the patient and his quality of life as a whole.⁹

Kim *et al.* developed a method for the calculation of the estimated life expectancy based on SSA life tables. For using this method as accurately as possible, some values have to be estimated. The author suggests that a lead time of 10 years can be achieved if a PSA test is performed, however, if the patient is considered not to be on the middle quartile of health, this value should be considered as 0. In this case, the health quartile is a system that separates patients into 3 categories, based on their overall health. If a physician considers a patient to be very healthy, that patient is placed on the highest quartile of health, which represents about 25% of a population. On the other hand, if a physician considers a patient to not be healthy, that patient is instead on the lowest quartile of health, which also represents about 25% of a population. Patients who do not fit either of these categories, and are considered overall healthy, are placed on the middle quartile, which represents about 50% of the population. By estimating both these values, and also the assessing the patient's age and GS, this method can estimate the life expectancy of a prostate cancer patient.³²

2.3 Treatment modalities

For prostate cancer, several healthcare professionals are involved on deciding the treatment course, such as medical oncologists, surgeons and radiation oncologists.³⁵ Nowadays, a great number of guidelines based on clinical evidence and clinical trials of large scales are available.³⁶ As a good amount of treatment options do exist, for finding the most suitable treatment option for a specific patient, several variables have to be taken into account. These variables include not only the presence of symptoms, adverse features and the patient's life expectancy, but also the risk of progression, risk of side effects, hospital resources, human resources and available technology, among others.^{8,11,35,37} Besides the mentioned variables, the literature widely supports physicians to take into account several other aspects, such as patient comorbidities, preferences and life styles, in order to engage in a system of shared decision making between the patient and the medical team. The following treatment modalities have been highlighted as first line approaches with the best results supported by evidence, and so, are considered the standard of care for prostate cancer:^{8,9,23,35,37-39,10-17}

- Observation;
- Active Surveillance (AS);
- Surgery;
- External Beam Radiotherapy (EBRT);
- Brachytherapy (BT);
- Androgen Deprivation Therapy (ADT).

2.3.1 Observation

Observation, also known as watchful waiting, is the approach where the patient's disease is and palliative treatment, usually ADT, is delivered when the disease becomes symptomatic or symptoms are imminent. The imminence of symptoms can be predicted by changes detected on PSA levels or physical exams.⁹ The purpose of this therapeutic approach is to maintain the patient's quality of life by avoiding unnecessary treatment when the patient has one or several comorbidities that will likely cause mortality sooner than the tumor itself.²⁵ Because of that, as opposed to AS, Observation is only a viable option to elderly or frail men with one or more comorbidity(ies) that likely will out-compete prostate cancer cause of death.^{9,11,13,40}

The protocols of this therapeutic approach involve only PSA tests and physical exams, excluding any kind of radiological imaging. Due to the side effects of biopsies, patients undergoing Observation should not be submitted this kind of procedure, and less invasive courses of action should be considered.⁹

A PSA test, as explained on chapter 2.1.3, consists on taking a blood sample from the patient and measuring the concentration of the PSA enzyme on the serum.²⁶ This test is performed routinely on both AS and Observation, since changes on the test's value can be indicative of disease progression, and may serve as a definitive sign that curative treatment, in the case of AS, or palliative treatment, in the case of Observation, should be initiated.⁹

A DRE is a non-invasive test that allows a doctor to physically check a patient's lower rectum and prostate, in only a few minutes.⁴¹ This exam allows the evaluation the size of the prostate gland and the presence of any lumps or abnormalities on the rectum and lower colon. Any physical abnormalities or changes can be easily noted by this procedure, so this constitutes a good mean to assess if further matters of screening are necessary for the time being. This is an easy and non-invasive procedure, that has no side effects if done correctly, and provides valuable information without any direct downsides.⁴¹

2.3.2 Active surveillance

AS is an alternative approach where the evolution of the disease is closely monitored, with the aim of delivering curative treatment if there are any signs of progression. This means that as soon as the symptoms begin or become imminent, a curative course of treatment is started. The main goal of this approach is to defer treatment and its potential side effects, specially urinary, bowel and sexual function.^{5,9,11,35,42} Because of both these aspects, this approach is mostly indicated for younger men with asymptomatic tumors and a low-risk disease.^{9-14,35,42} Since these patients have longer life expectancies, they should be followed closely and treatment should start as soon as the disease progresses, so cure rates are not compromised.⁹ AS is also a viable option for patients with asymptomatic diseases who are eligible for curative treatment, but that for some reason, refuse curative treatment. Patients with family history of aggressive prostate cancer are not good candidates, as the disease is expected to progress and spread on faster rates.¹¹ AS protocols usually include these 4 courses of action: PSA test, mpMRI, digital rectal exam (DRE) and biopsy.^{5,9,11,13,14,16,17,42}

Magnetic Resonance Imaging (MRI) is a non-invasive imaging exam that produces a three-dimensional image of a patient's pre-determined body part or Region Of Interest (ROI).

Traditionally, for the assessment of the prostate gland, T2-weighted MRIs are used. In this kind of imaging, the water located on the patient's tissues is reflected on the image, which allows a good visualization of the peripheral zones and zones of transition of the prostate gland, which are made of soft tissue.⁴³

As for mpMRI, by multi-parametric, is stated that images should be acquired with at least an additional functional form of MRI, to supplement the traditional T2-weighted images.⁴³⁻⁴⁵

The most commonly used functional sequences for prostate cancer screening are Dynamic Contrast-Enhanced (DCE) MRI and Diffusion-Weighted (DW) MRI. Since most commonly used T2-weighted MRIs are not suitable by themselves to diagnose tumor aggressiveness, by combining at least two sources of information, it is possible to better detect the tumor presence and location within the prostate gland, and also to delineate its borders and angiogenesis, hence allowing the physician to get better sense of aggressiveness.^{43,44,46} DW MRI is an MRI modality which allows the visualization of the flow of water molecules. Since prostate cancer has increased cell density, DW images capture the tumor as an area where the flow of water is restricted, allowing the better assessment of the tumor's location.⁴⁵ DCE MRI are MRI images acquired after an intravenous injection of a contrast agent, such as gadolinium. This gives a better visualization of the vascular areas in the prostate areas, which is useful since abnormal neovascularity is usually a sign or indication of cancer.⁴⁵

During the acquisition of an MRI for diagnostic purposes, the patient is positioned in supine position on the scanner's couch top and should remain still while the image is being acquired, using suitable positioning devices for both stability and comfort.⁴⁷ Due to the machine's magnets, patients containing metallic objects on their body, such as pacemakers or prosthetics, are not good candidates for MRI and other methods of imaging should be considered.⁴⁸

A biopsy is a procedure that allows the histologic assessment and tumor aggressiveness evaluation through the analysis of a sample of tissue taken directly from a suspicious area of the disease. Biopsies performed to assess prostate cancer are performed using a small needle that will be used to take sample(s) of the prostatic tissue. The sample(s) are then analyzed on the microscope by a pathologist to determine a number of displayed characteristics, such as GS, tumor histology and other parameters that allow staging and aggressiveness assessment. Prostate biopsies are generally done in one of two ways: by a trans-rectal ultrasound (TRUS) guided approach or by a transperineal approach. On both approaches, a sample of the seminal vesicles can also be taken in order to assess SVI, since this is the main region to where prostate cancer progresses first. Biopsies are associated with several side effects, such as pain or discomfort on the rectum, due to the placement of the US probe, or on the anatomic region where the needle was inserted. In the following weeks after the procedure, local bleeding could also occur, and traces of blood are usually found on urine, feces or semen. Besides those, acute urinary retention could also happen due to the swelling of the prostate, as well as erectile dysfunction due to the damage done on the nerves. These symptoms are not permanent and should improve over time. As for risk of infection, antibiotics are prophylactically prescribed in order to prevent this issue.

2.3.3 Androgen deprivation therapy

Androgens are steroidal hormones mainly produced by the testicles and adrenal glands. The most common androgens produced on the male body are testosterone and dihydrotestosterone. The goal of ADT, also known as hormone therapy, is to reduce the concentration of androgens, which stimulate the growth of the glandular prostate cells and serve as fuel for these kinds of tumors.⁴⁹

In concordance, lowering androgens levels or simply blocking them, impedes tumor growth and may reduce its total size. Despite the advantages, ADT alone is not sufficient to eradicate the disease. Because of that, ADT is mostly use as neoadjuvant, concurrent or adjuvant approach to another principal therapy, such as surgery or EBRT.⁴⁹ However, radical ADT can be applied to high and very high risk patients with a life expectancy inferior to 6 years, but usually other treatment approaches, with higher successful rates, are preferred.⁹

Most of the side effects of this treatment are due to the lack of testosterone production, such as decrease of desire for sexual activity, fatigue, hot flashes and muscle loss. Some of this effects can be attenuated by taking testosterone supplements.^{11,50} Other less common side effects may occur, like breast tenderness or growth, osteoporosis, anemia, weight gain and increase of cholesterol levels, which usually decrease when the treatment stops, if a non-permanent approach is chosen.⁴⁹

2.3.3.1 Bilateral orchidectomy

Bilateral orchidectomy is a surgical procedure where both testicles are removed.^{5,49} As testicles are the main organ responsible to produce androgens, removing them causes the tumor to stop growing and reduce its size. In this procedure, a small incision, either on the scrotum or on groin, is performed, in order to cut the spermatic cord and removing the testicles. The removed testicles can be substituted with a prosthetic in order to retain the aesthetics.^{50,51} This is most unexpansive approach and does not require hospitalization. However, the patient becomes sterile, even though erection is still possible, and the treatment is permanent, as opposed to other ADT modalities.⁴⁹ A representation of the procedure can be visualized on annex 9.⁵¹

2.3.3.2 LHRH agonists

Luteinizing hormone-releasing hormone (LHRH) agonists are a group of medical drugs that reduce the amount of androgens produced by the testicles.^{5,49} Natural LHRHs are produced on the hypothalamus and stimulate the production of the luteinizing hormone (LH) by the pituitary gland, which stimulates the Leydig cells on the testicles to produce testosterone.

The testosterone production functions as negative feedback on the hypothalamus, in order to maintain normal testosterone levels. By using synthetic LHRHs agonists, it is possible to saturate the LH receptors on the pituitary gland, since they compete with the natural LHRH agonists to bind to the LH receptors.⁵ This approach initially raises the testosterone production, but when the LH receptors saturate, the produced testosterone stops the production of LH on pituitary gland by negative feedback mechanisms. This stops the stimulation of testosterone production by the Leydig cells and eventually lowers the androgens concentration to levels compared to a bilateral orchidectomy.⁴⁹

As this is not a permanent therapy, this approach is the most preferable to patients. Although the testicles are not removed, they may shrink in size.⁴⁹ This approach allows the reverse of the side effects when the treatment is stopped the employment of intermittent ADT regiments., while avoiding the trauma of an invasive surgery and the removal of testicles.⁵

The most common LHRH agonists use for prostate cancer therapy are Leuprolide, Goserelin, Triptorelin and Histrelin, which can be administered by an injection or by an implant placed subcutaneously, from once a month up to once a year.^{5,9,49}

Added to LHRH agonists, non-steroidal antiandrogens act as blockers for the testosterone, impeding the binding of androgens to the androgen receptors on the prostate gland.^{5,49} This drugs are usually used in concomitance with LHRH agonists in order to reduce the initial raise of the testosterone production, while also reducing the occurrence and intensity of the sexual side effects of ADT.^{5,9,49}

The most common non-steroidal antiandrogens used for prostate cancer treatment are Flutamide, Bicalutamide and Nilutamide, which are taken as daily pills.^{5,9,49} The use of Flutamide should be limited due to the gastrointestinal side effects, and Bicalutamide is not indicated for metastatic disease, so between the three, Nilutamide is the most popular choice.⁵

2.3.3.3 LHRH antagonists

Rather than competing with the natural LHRH agonists, the LHRH antagonists act as blockers to the LH production, by impeding the binding of the LHRH to the LHRH receptors on the pituitary gland.⁵ The advantage over the LHRH agonists is that this approach allows a faster reduction of the testosterone levels, without the initial raise of the concentration of androgens, to levels compared to bilateral orchidectomy.^{5,49} Besides that, it also allows the reverse of the side effects, the employment of intermittent ADT regiments, while avoiding the trauma of an invasive surgery and the removal of testicles.⁵

The most common LHRH antagonist used for prostate cancer treatment is Degalerix, which is administered once a month by a subcutaneous injection.^{5,9,49}

2.3.4 Brachytherapy

BT is an RT modality where instead of the treatment being delivered by a radiation source located externally to the patient, it is instead delivered by one or more radioactive sources placed directly on the tumor. For prostate cancer, this is usually done in one of two ways, by either using a low-dose-rate (LDR) approach, or a high-dose-rate approach (HDR).^{9,52,53}

As stated on appendix 2, both LDR and HDR approaches use radioactive isotopes with low mean photon energy.^{42,52} By placing the radioactive source(s) as close as possible to the tumor using interstitial implants, given the low range of the radiation beam, it is possible to scale the dose delivered to the tumor while sparing the OARs, since the radiation beam originated by the source's decay has not enough penetration power to reach distant organs. Because of this advantage, BT for selected patients has a similar outcome to RP but with better tolerance of treatment, since this approach is not as invasive.⁴²

While radical BT is only indicated for localized disease, since it does not allow the irradiation of the regional lymph nodes, it can instead be used as a boost after primary EBRT for irradiation the pelvic lymph nodes, either with or without ADT, having similar results to radical EBRT.^{9,11,14} The principal OARs are the rectum, urethra, bladder and penile bulb and as for side effects, the most common are incontinence, diarrhea, urinary stricture, impotence and proctitis.^{42,53}

2.3.4.1 Low-dose-rate brachytherapy

LDR BT is a variant of BT, where the dose delivered to the tumor by the radioactive isotope is delivered in a low rate and over time. For prostate cancer, this means the radioactive sources, typically seeds, are permanently placed on or next to the tumor, irradiating the whole prostate gland and a few millimeters around it.^{11,13,53} The sources eventually decay completely and stop emitting radiation, and since there is no hazard in leaving them on the patient's body, they are left there as to avoid any unnecessary procedures.⁵³ The most common isotopes used for this procedure are Iodine-125, Palladium-103 and Cesium-131.^{9,13}

The treatment is planned using TRUS images and GTV is defined as the whole visible tumor, while the CTV is defined by applying a margin of 3 mm to the GTV, with a 0 mm margin posteriorly. For this approach, there is no need to define a PTV and the treatment dose is prescribed to the CTV. The OARs are usually the rectum, bladder and urethra.⁵

During this procedure, an US probe is inserted through the patient's rectum and located above it is a template that will assist the physician to precisely insert the seeds in the prostate gland. With the template placed on front of the perineum, hollow catheters containing each a small radioactive seed are placed on a predetermined location of the prostate gland based on the TRUS images.

The sources are *manually afterloaded*, using any additional tools necessary for handling and placing them, like hollow needles.^{5,52} The procedure is finished after 60 - 100 seeds are placed, which usually takes from one to two hours. An example of this setup can be visualized on annex 7.⁵³

This procedure usually requires the patient to stay hospitalized only for one night and is considered to be less invasive than a RP. Since the treatment is all done in one fraction, it does not require the patient to do daily visits to the hospital, like in EBRT courses. It also has a lesser risk of permanent side-effects and has a higher probability of preserving the patient's erectile function.

Despite all these advantages, this technique requires special resources and trained staff, which is not available in every facility. Prolonged urinary side-effects may still occur and there is also risk associated with anesthesia and the surgical procedure of placing the seeds. It is advised for the patient to avoid physical contact with children and pregnant women for two months, and during the first ejaculations a condom must be used due to possible seed migration.⁵³

2.3.4.2 High-dose-rate brachytherapy

HDR BT is a variant of BT where the dose delivered to the tumor by the radioactive isotope is delivered at a high rate and over a short time. For prostate cancer, it means the radioactive source is placed through temporary catheters, which remain on the target volume for shorter periods of time.^{11,13,53} The most common isotope used for this procedure is Iridium-192.^{9,13} As opposed to LDR BT, HDR BT is often used concomitantly with other therapies, such as ADT and/or EBRT.⁵³

Treatment planning can be done either with TRUS, CT or MRI images and since this treatment is not susceptible to setup uncertainties, as the target volume is immobilized by the catheters and treated with short treatment times, it is not necessary to define a CTV or PTV, and the target volume is defined as the GTV, being the whole prostate gland.⁵

Similarly, to the LDR approach, a template is placed on the patient's perineum and through this template catheters containing radioactive sources are inserted, until they reach the desired destination on the prostate gland. Usually 15 to 25 catheters are used, and they remain on its location until the treatment ends, which may take a few hours. The catheters are connected to a machine that will *remotely afterload* the radioactive sources, travelling automatically from an external shielded machine through the catheters until they reach their destination.

After the treatment is delivered, they are automatically collected, without needing any manual handling.⁵² An example of this setup can be visualized on annex 7.⁵³ The treatment itself only lasts a few minutes, but the whole procedure may take a few hours.⁵³

Compared to EBRT, HDR BT has shorter treatment times as it is usually delivered in one or two fractions, with minimal immediate side effects and minimal recovery time. Regardless, a short stay in the hospital is still necessary and the patient needs to stay still with the catheters placed, sometimes overnight, and a spinal anesthesia also needs to be applied. Long term side effects can affect the bladder, bowel and erectile function.⁵³

2.3.5 External beam radiotherapy

RT is a non-invasive treatment modality that delivers, to a specific target volume, high doses of ionizing radiation, in order to kill the cancerous cells and stop their ability to grow and divide, by damaging their deoxyribonucleic acid (DNA). EBRT delivers the treatment with a source of radiation located externally to the patient's body, such as Linear accelerator (Linac).⁵⁴ As a treatment modality, EBRT is the standard elective treatment for prostate cancer, with long-term results similar to RP.^{12,37,52} However, patients who had prior pelvic irradiation, who have inflammatory disease of the rectum, permanent indwelling Foley catheter, very low bladder capacity, chronic moderate or severe diarrhea, bladder outlet obstructions requiring a suprapubic catheter or inactive ulcerative colitis, are not suitable candidates for EBRT.^{9,11}

This modality has low risk of urinary incontinence and stricture and can preserve the erectile function of the patient. It also avoids complications related to a surgical procedure, such as bleeding, transfusion-related effects and risks associated with anesthesia.

Nonetheless, this modality also has some disadvantages associated. The treatment course lasts 8 to 9 weeks and up to 50% of the patients develop temporary bladder or bowel symptoms, there is also risk of developing radiation proctitis, erectile dysfunction and rectal complications.⁹

2.3.5.1 Basic principles of radiation oncology

On a time-scale, the interaction between ionizing radiation and the tissues of the human body occurs in three consecutive phases.⁵⁵

On the first phase, called the physical phase, as the radiation passes through the tissues, it interacts with electrons on the atoms' orbits by Coloumb interactions. By doing that, some electrons are ejected, and the atom is ionized. The radiation can also transmit energy to these atoms, putting them on an exciting state. If the ejected electrons are provided sufficient energy, they can excite or ionize nearby atoms, creating a sequence of ionization events.^{55,56}

On the second phase, called the chemical phase, the ionization and excitement of atoms leads to the formation of free radicals, which are molecules with unpaired electrons that are highly interactive as they mean to restore their charge equilibrium.⁵⁵ Since the human body is mostly constituted of water, the most common free radicals are the water ion (H_2O^+) and hydroxyl (OH^*). If oxygen is present on the cells, the amount of produced free radicals, specially superoxide (O_2^-), should be proportional higher. When free radicals reach the nucleus of the cell, they tend to interact with the hydrogen atoms of the deoxyriboses of the DNA molecules, dealing damage to the cells.^{55,56}

On the third phase, called the biological phase, the chemical damage done on the cells on the previous phases is repaired, if possible. However, the damage done cannot always be repaired and sometimes leads to cell death.

In practical terms, radiation can induce several effects on the cells, such as:^{55,56}

- No impact at all;
- Delay cell division;
- Cause cell death before it can divide;
- Cause cell death when they attempt to divide;
- Cause mutations on the cells;
- Produce a bystander effect, which is when an irradiated cell sends chemical signals to nearby cells that will damage them;
- Make the irradiated cell more resistant to radiation.

The α/β ratio is a combination of two parameters that are used on the Linear Quadratic Model (LQM) to describe the effects on ionizing radiation on cellular tissues. The parameter α is related to the unreparable damage done to the cells, while the parameter β is related to the repairable damage done to the cells. The ratio of both parameters, α/β , is the representation of the protentional of repair for cells irradiated with a fractionated dose. Tissues that exhibit early reactions to radiation exposure, have higher α/β values, in a range of 7 – 20 Gy. On the other hand, tissues that exhibit late reactions to radiation exposure, have lower α/β values, in a range of 0,5 – 6 Gy. This notion roughly translates to tissues who have higher α/β values being more sensitive to radiation, while tissues who have lower α/β values being less sensitive to radiation, and by consequence higher ability to repair between treatment fractions. Since tumors have higher α/β values, by separating the total treatment dose in fractions with smaller doses, it is possible to reduce the damage done to healthy tissues while delivering a treatment dose to a tumor. The radiosensibility of prostate tumors can be described with an average α/β value of 1,5 Gy, while the healthy tissues have an average α/β value of 3 Gy.⁵⁷

In RT, the amount of radiation (dose) delivered to a patient, is measured in Gray. Gray, abbreviated as Gy, is the International System of Units measuring unit for absorbed dose, and represents the amount of energy of ionizing radiation absorbed in a unit of mass. 1 Gy is equivalent to 1 Joule per kilogram (J/kg).⁵⁸

2.3.5.2 Dose fractionation

RT Treatments are often delivered in a conventional fractionation regimen. This means that the total treatment dose is split equally on fractions of 1,8 or 2,0 Gy, which are delivered in 5 days per week, until the total prescribed dose is achieved.^{9-11,37} This regimen is mainly used since, theoretically, normal healthy cells have lower α/β values in comparison to tumor cells. By delivering the treatment in smaller daily doses, interrupting 2 days a week, usually on weekends, it allows the radiation to kill the cancerous cells while giving the healthy cells time to repopulate, limiting side effects by damage done on healthy tissues. Besides that, since this fractionation regimen is the most globally used, its side effects are more well-reported and known, comparing with other fractionation regimens.¹³

Opposed to conventional fractionation, hypofractionation is a regimen where treatments are delivered in daily fractions with doses greater than 2,0 Gy. Studies suggest that the α/β value of prostate tumors is lower than the α/β value for the bladder and rectum, but the difference in both values is not substantial. This means that prostatic tumors are more sensible to the increase of the dose delivered in each fraction than the healthy tissues themselves. The shorter the α/β value of the prostate is estimated to be, the more the dose per fraction can be increased. Therefore, the dose per fraction can practically be increased without having the risk of critically increasing the dose on the nearby healthy tissues like the bladder and the rectum.⁵⁷ Because of that, hypofractionation is, in theory, more effective than conventional fractionation for the treatment of prostate cancer, and has been proven that improves successful rates of the treatment.^{5,13,37,55} Besides the clinical advantages, this regimen also shortens total treatment duration, which is more convenient to patients, uses less resources and is more cost-effective, while producing similar results when compared to conventional regimens delivered with Intensity Modulated Radiotherapy (IMRT).^{9,10,37}

Moderate Hypofractionation is a type of hypofractionation where the dose delivered each fraction ranges between 2,4 and 4 Gy, while Extreme Hypofractionation, also known as Ultrahypofractionation, refers to when the treatment is delivered in fractions of 5 to 15 Gy.^{10,13,37} Extreme hypofractionated regimens should only be delivered when in combination with Stereotactic Body Radiotherapy (SBRT), due to the precision needed when dealing with higher doses of radiation, in order to avoid unnecessary radiation damage on healthy tissues.¹³

2.3.5.3 Treatment techniques

For prostate cancer treatments, typically a beam of x-rays (photons) is used, which is produced by a particle accelerator called the linac. A visual scheme of the linac and its components can be consulted on annex 6. A photon beam has an adequate penetration power and is able to reach deeper locations within the human body, such as the prostate gland.^{52,58} Conventionally, for the treatment of pelvic malignancies, energies between 10 – 20 MV are applied. However, with current technology, beam energies above 15 MV are to be avoided due to the formation of neutrons, which may create some radiation protection issues.⁵⁸

Localized prostate cancer EBRT treatments demand high conformal dose distributions in order to avoid an excess of dose to the Organs at Risk (OARs). This means that the delivered dose should be as restricted as possible to the tumor, while sparing as much as possible healthy tissue. In order to achieve this goal, highly conformal techniques are preferred.^{9,37}

3D-Conformal Radiotherapy (3DCRT) was the first treatment technique to use a computerized software to integrate the information of the patient's anatomy on a Computed Tomography (CT) scan with the capabilities of the treatment machine, to allow the creation of a treatment plan. In this technique, the number, position and shape of the radiation beams are defined by the dosimetrist or physicist, so the predefined criteria to achieve dose escalation on the target volume(s) while sparing the surrounding healthy tissues are met. The shape of each beam is defined by a Multi-Leaf Collimator (MLC) located at the end of the linac's gantry, which statically stays the same for the beam-on time of each beam.⁹

IMRT uses a combination of radiation beams, or arcs in the case of Volumetric Arc Therapy (VMAT), to provide an even higher conformal dose distribution in comparison with 3DCRT. With IMRT, the beams or arcs are heterogeneous, and their intensity is variable, in the way that better fits the designed needs. For both these techniques, an inverse planning is applied, meaning that based on numerical dose constraints and goals, a computerized algorithm on the Treatment Planning System (TPS) arranges the number, position, shape and fluence variation of the radiation beams or arcs, using a dynamic MLC to adapt the dose distribution to the target volume. Over 3DCRT, IMRT techniques have the advantage of reducing the risk of gastrointestinal toxicities.^{9,11} The main advantage of VMAT over IMRT is shorter treatment times, as treatments are delivered in a continuous form with few interruptions. Both techniques allow adequate dose distributions regarding the concave shape of the prostate, which helps to minimize the dose on critical OARs such as the rectum.¹³

On the other hand, SBRT is an EBRT technique where the treatment is delivered by stereotactic guidance, on an extracranial target, providing a highly conformal dose distribution in a less than 5 fractions.^{9,59}

For stereotactic treatments, a stereotactic frame that defines a fixed coordinate system, will be used to locate the target volume in all treatment fractions.⁵⁶ Given that a high dose of radiation is being delivered in few fractions, and the maximum tolerable uncertainty is ± 1 mm, the treatment margins need to be slimmer when compared to IMRT or 3DCRT, since there is a bigger risk of providing damage to the healthy tissues. Besides that, the patient and the prostate gland need to be immobilized in a way that guarantees that deviations on the target volume superiors to 1 mm will not occur, so healthy tissues are not harmed. For those reasons, SBRT gives the exact precision necessary for the safe delivery of extreme hypofractionated regimens. Also because of the need for smaller margins, SBRT is only indicated for the treatment of small volumes, since bigger volumes usually need bigger margins due to deviations on its positions. However, SBRT is only a viable option if the RT department has the appropriate technology and expertise, such as a precise image-guided delivery system.^{9,11,56}

2.3.5.4 Treatment preparation and planning

A CT scan is the optimal solution to acquire detailed information regarding the patient's anatomy, since it allows the detection of gross extracapsular disease, metastasis on lymph nodes and also distant metastasis.⁹ The CT scan does not only give anatomical information about the patient's body, but also gives information regarding the electronic density of the body tissues, which allows the use of a TPS to elaborate the best treatment plan possible for a given patient, having an indication of how that treatment plan will manifest itself on the patient's body, in the form of a dose distribution.⁶⁰

It is during the planning CT that the position of the patient for the treatment is decided, which should be reproducible and comfortable enough for the patient to be able to withstand it during the whole treatment, while exploring any possible dosimetric advantages that different positions may have. Patients can either be positioned on prone or supine positions. Prone position has the advantage of decreasing the dose delivered to the rectum and bowel, by pushing the small bowel off the treatment area, avoiding additional gastrointestinal toxicity. However, a greater percentage of bladder volume may be irradiated as this position is more susceptible to errors due to patient discomfort. Opposed to that, the supine position is the more common approach, since it is more stable and reproducible for the patients, assuring comfort and stability with acceptable results when using highly conformal treatment techniques.^{10,38}

Patients should also be put on an antifatulent diet and milk of magnesia laxative in order to decrease gas on the bowel. This not only reduces setup errors but also the total volume of the rectum, decreasing the volume of healthy tissue to be irradiated.

As for the bladder, it should be comfortably full, as it helps to physically push the rectum as much as possible away from the target volume.^{10,38,39}

If extra immobilization is necessary, for example for SBRT techniques or extreme hypofractionated regimens, endorectal balloons can be used to reduce prostate movement. These work by keeping the rectum in place and at a constant volume, which allows that invariable volume to be taken into account while doing the treatment plan, to avoid as much radiation as possible to the rectum.^{10,38} In the same chain of thought, perirectal spacers can also be used to achieve this mean. These devices are made of a foreign material that is placed surgically between the rectum and prostate in order to clearly separate these two organs, providing additional target immobilization and reducing total rectal toxicity. When there is rectal invasion, clinical stage T3 or posterior extension, this method is not recommended.^{9,10}

Volume contouring on the planning CT is mandatory in order to avoid under and over dosage of the target volume(s) and OARs. Using an algorithm provided by the TPS, it is possible to predict how much dose is going to be delivered on each ROI, and optimize the treatment planning in order to achieve the best dose distribution possible and avoid toxicity.³⁹ The Gross Tumor Volume (GTV) is contoured as the tumor volume seen on the planning radiological images. For prostate cancer, the GTV is usually defined as the entire prostate gland and any visualized extension, including or not regional lymph nodes and/or distant metastasis.^{10,37,38} The Clinical Target Volume (CTV) represents the GTV plus the areas of risk of subclinical disease, including or not the seminal vesicles, the extraprostatic extension and the pelvic lymph nodes. For low risk patients, the CTV usually matches the prostate gland and seminal vesicles, which might equal the GTV. For intermediate and high risk patients an isotropic margin of 5 mm is often used, although the proximal margin can be extended to 1 cm or 2 cm respectively.^{10,37,38} Lastly, the Planning Target Volume (PTV) represents a margin of typically between 0,5 to 1 cm added to the CTV, which accounts for patient movement, setup errors and organ movement. As for the OARs, these often include the rectum, anus, bladder, penile bulb, bowel bag and proximal femurs. Since they are the closest to the treatment site, their irradiation is also the principal cause of toxicity and side effects, so contouring these organs is of extreme importance.^{10,38}

2.3.5.5 Treatment delivery

Image Guided Radiotherapy (IGRT) is a modern variation of EBRT where the target volume(s)' position is verified daily by using any imaging means accessible on the treatment unit, either before, during, after, or during all phases of the treatment delivery, allowing the verification of the volume of the bladder and rectum, which should be consistent with the planning CT.⁵

IGRT is also essential in order to reduce the treatment margins and spare the OARs, since reducing the setup error allows the reduction of the PTV margin and therefore, allows a safer dose escalation which improves biochemical outcomes and reduces treatment toxicity.^{9,10} When dose escalating, the organ movement and setup errors become an issue, so organ movement should be visualized and corrected on-line via IGRT, using one of the following methods: CT, US, fiducial markers or electromagnetic tracking. Despite the advantages, radiological imaging use should only be used when medically justified as it may oblige to the delivery of additional ionizing radiation to the patient.^{9,10,13}

2.3.5.6 Prophylactic irradiation of the pelvic lymph nodes

For primary EBRT in localized prostate cancer, the pelvic lymph nodes can be prophylactically irradiated when there is suspicion of undetectable lymph node metastasis. On contrary to total treatment doses, which are highly variable, the prophylactic lymph node irradiation is typically performed with a standard range of doses between 45 and 50,4 Gy, delivered in fractions of 1,8 – 2 Gy (conventional fractionation), with either 3DCRT, IMRT or VMAT.⁹

Stereotactic techniques and hypofractionation are not indicated for lymph node irradiation, due to the target volumes being of greater sizes, which implies the need for bigger treatment margins that go outside the safety tolerances. If there is a necessity to irradiate the pelvic lymph nodes, either prophylactically or curatively, the treatment should be split in two or more phases. In the first phase, the pelvic lymph nodes are irradiated with conventional fractionation, and in the second phase, the prostate gland, including or not the seminal vesicles, may be irradiated with an hypofractionated regimen.^{11 9,37}

According to guidelines, pelvic lymph nodes should not be irradiated for very low and low risk patients and should only be irradiated in intermediate risk patients if the disease displays adverse features. As for high and very high risk patients, prophylactic lymph node irradiation should be strongly considered.^{9,11,13,16}

2.3.6 Radical prostatectomy

RP is a procedure where the whole prostate gland, and a surrounding tissue margins, are surgically removed. If SVI is suspected, the seminal vesicles can also be resected during the procedure. It is important to consider nerve-sparing techniques, in order to allow the patient to retain as much function as possible. The patient may either be submitted to local anesthesia, such as epidural, or general anesthesia.⁶¹ A representation of the male anatomy before and after a RP procedure can be visualized on annex 2 and 3 respectively.⁶²

RP is only indicated for tumors restrained to the prostate gland, on patients with longer life expectancy, since this is a highly invasive procedure. This procedure is more commonly used on early stage tumors, but some high and very high risk patients may benefit from RP, especially when the disease is recurrent after primary EBRT.^{9,11}

There are several complications associated with a surgical procedure by itself, such as bleeding, transfusion related effects and risks associated with anesthesia, like myocardial infarction and pulmonary embolus. Besides those, the most common side effects of RP, not directly related to the surgical risk, are urinary incontinence or leakage, erectile dysfunction and sterility.^{42,61}

In general, RP can be performed using one of the following techniques:^{5,9,11,42,52,61}

- Suprapubic incision;
- Retropubic incision;
- Perineal incision;
- Laparoscopic;
- Robotic-assisted laparoscopic.

A RP performed with a suprapubic incision is a surgical procedure where the incision is performed above the pubic bone of the pelvis and through an opening in the bladder. On the other hand, a RP performed with a retropubic is a surgical procedure where the incision is performed in a location lower than the pubic bone, and not through an opening in the bladder. In both approaches, after performing the incision, the surgeon proceeds to remove the whole prostate gland and surrounding tissues that might contain microscopic disease, which may also include the seminal vesicles.⁶¹ A representation a retropubic incision performed on RPs can be consulted on annex 4.⁶³

If the perineal approach is preferred, an inverted u-shaped incision is performed on the perineum, and through that incision, the prostate gland and any suspicious tissue on the perimeter will be removed.⁶¹ A representation of a perineal incision performed on RPs can be consulted on annex 4.⁶³

On the laparoscopic approach, instead of a wide cut, several small cuts are done on the patient. In one of the cuts is placed a laparoscope, which will be used as visual guidance for the procedure. On the rest of the cuts, are placed the tools that will assist and perform the surgery. This allows the physician to visualize the patient internally while manipulating the tools that will allow the removal of the prostate gland. Besides being done manually, this can also be done using a robotic system, such as a robotic arm, which is controlled in real-time by the surgeon.⁶¹ A representation of the incisions performed on a laparoscopic RP can be consulted on annex 5.⁶²

2.3.6.1 Pelvic lymph node dissection

Pelvic Lymph Node Dissection (PLND), also known as pelvic lymphadenectomy, is a surgical procedure where the lymph nodes located on the pelvis, such as the internal, external and common iliac nodes, are removed. PLND is the most precise way of diagnosing the presence of metastasis on the lymph nodes. Adding to that, it is as well the most precise way for treating infected lymph nodes, and can also give valuable information when adjuvant therapy is being considered.⁶⁴

The procedure itself can either be done with a wide cut or laparoscopically, at the same time as the RP or as an isolated procedure. The excised nodes are then sent to be examined by a pathologist, to determine if metastases are present or not.⁶⁴ An extended PLND, will in fact cover more area and so has a higher probability of discovering lymph node metastasis and eradicate any undetectable micrometastases, so this kind of approach is often preferred.^{9,65} An extended PLND is performed by removing all the node-bearing tissue confined to these limits:^{9,14}

- Anterior: External iliac vein;
- Lateral: Pelvic sidewall;
- Medial: Bladder wall;
- Posterior: Floor of the pelvis;
- Distal: Cooper's ligament;
- Proximal: Internal iliac vein.

The most common complications associated are lymphocele, thromboembolic complications, neurological injury, ureteral injury, vascular injury and lower extremity edema.⁶⁵

2.4 Clinical decision support system

The process of decision making regarding a medical workflow can not only be made by intuition, as this can lead to choosing unpredictable and unreproducible courses of action with unknown consequences.² Clinical guidelines act as a summary of the most innovative and evidence-based research on a given medical subject. They lead to the standardization of procedures, through research and medical trials, which enables the avoidance of unnecessary medical errors and suboptimal results.^{2,66}

Two of the greatest issues in standardizing medical procedures are the discrepancy on the protocols employed on different hospitals and healthcare centers and the difficulty on sharing information in an efficient way, and in a language available and easy understand by the global healthcare community.

To overcome these issues, guidelines are to be made by clinical experts and should be easily available and supported by relevant and cleverly chosen clinical trials.^{3,66} As these documents are usually available in reports or booklets consisted of several very information-dense pages, it is easy for healthcare professionals to feel overwhelmed when there is the need to be aware of the numerous current practices for every patient, which happens regularly. When this issue is present, the objective of the guidelines is contradicted, and they tend not to be followed and the flow of information is interrupted, since it is not being facilitated.⁶⁶

In medicine, a clinical DSS is a practical tool to assist a healthcare professional to make a decision regarding a patient's diagnosis or course of action, facilitating the management of complex and uncertain possibilities.^{1,2,4,8,67} Using multiple variables assessed by a competent user, such as patient demographics and disease characteristics, the system's algorithm generates a report specifically meant to a specific patient, summarizing information regarding the most indicated course of action for a specific disease. It has been proven that the number of variables a person can take into account simultaneously to make a decision is limited to 5, but on the other hand, when confronted with a situation where a decision has to be made, humans also have the ability to access stored information in a way that it becomes rapidly accessible when a similar situation is presented.⁸

In the context of precision medicine, which means treating the right person, with the right treatment and at the right time, both these skills are necessary to rapidly access all the possible options and choose the best suited one, taking into account previous experiences with patients with similar conditions, which were treated with good outcomes, and the well reputed information accessible worldwide.¹ In its greatest extent, a clinical DSS will stimulate the following of good medical practices and therefore improve physicians' performance, patient outcomes, clinical workflows and also provide a saving in hospital resources, work productivity and waitlists, among others.^{2,66}

A Knowledge-based clinical DSS is a digital tool with the aim to provide information to an user, by means of active interaction between two types of information, such as the information on a knowledge base and the information provided by a user, instead of providing a definitive answer or making a definitive output all by itself. Knowledge-based clinical DSSs are usually built using three features: a knowledge base, a reasoning engine, and a mechanism of communication. Each of these features have a distinct function and will work in unison to provide trustable results.⁴

2.4.1 Knowledge base

The starting point of development of a clinical DSS is the knowledge base. Decision rules are often defined as the representation of knowledge and its flow of logic, that leads to the reason why a specific decision was made. They can be represented in the form of an algorithm, which is translated to chains of events that are called condition-action rules, and often use this format:

IF <condition> THEN <consequence>

This means that any given statement is followed by a consequence, and as long as the predetermined conditions are met, the statement is the consequence of the decision made by the user.^{3,4} When decision rules follow a specific flow, they can be graphically represented by decision trees or flow charts. Flow charts are visual representations of the available options and their outcomes, represented in a chain of events and follow a certain constant flow. On decision trees, each “node” represents one available option and the following “branch” is followed depending on the chosen option. The end of each branch represents the final output.^{2,3,68}

The main advantage of building a clinical DSS with a knowledge base organized in a flow chart format is that any programming language that supports routines, subroutines and functions can be easily used to convert medical knowledge in an executable workflow system. However, since the clinical information and the programming information will be mixed, this forces the developer(s) to dominate both clinical and programming domains, as both cannot be done independently. Besides that, if an update of the clinical information on the knowledge base is needed, which may oblige alterations on the decision rules, that may require extensive reprogramming, which may be very time-consuming and may lead to errors.³

2.4.2 Reasoning engine

The majority of clinical guidelines provide information not only of clinical practices, but also clinical workflows. The reasoning engine can be defined as the means used to combine the information stored on the knowledge base with the information regarding the patient, which is provided by the user. It is also essential for the cross-matching of information and purveyance of a definitive result, which will then aid the healthcare professional in making a decision.^{4,66} If the system is based on production rules, each bit of knowledge is stored in a form of an if-then statement, which are also called condition-action rules, and the reasoning engine, using the information put by the user, will decide which statement to execute in order to produce the desired consequence.³

As explained on the previous chapter, conditions represent logical statements that if proven truthful leads to the definitive consequence.³

Since a procedure is a sequence of conditions and consequences that occur one after the other, the reasoning engine needs to be able to understand when to interrupt the flow, for the user interaction, and when to restore it, knowing which statement should follow such interaction.³

2.4.3 Communication mechanism

The communication mechanism is the mean with which the user will interact with the system. It could be a software, a mobile app, a website, or other digital mean. The principal function of the communication mechanism is to provide the system a way to ask the user the information needed for the algorithm to satisfy its function, as well as a platform for the user to insert needed information. It is also through the communication mechanism that the system will generate and present the final output to the user, for example in the form of a report.⁴

2.4.2 Implementing a clinical decision support system

Practical guidelines can be put to practice as the knowledge base of a clinical DSS. In order to assure that the system is implemented in a safe and useful manner, and that it has protentional to provide its intended goals, some aspects have to be taken into account. As stated by Berner *et al.*, for a successful implementation of a clinical DSS this aspects need to be assured:⁴

- Users understand the clinical DSS limitations;
- The information available on the knowledge base comes from a reputable well-identified source;
- The system is appropriate for its intended use;
- Users are properly trained to efficiently make use of the system;
- Users are properly using the system, meaning that there is no margin for bad practice due to input errors;
- The knowledge base is managed, monitored and up to date.

These are the core aspects for a smart implementation of a clinical DSS with clinical value and reproducibility. It is also stated that the system should not only be focused on the user and on the result, but also on the process that leads to the decision-making and in future applications and improvements, which are mandatory due to the constant evolution of medical practices.⁴

2.5 Visual basic

Visual Basic (VB) is a programming language used to create Windows applications. VB is an object-oriented language where the developed software is designed around premade objects, such as text boxes and combo boxes. It also has an event-driven interface, where instead of the code being read from one end to the other, its execution can be activated by determined events, such as clicking a button or pressing a button on the keyboard.⁶⁹

While developing a software using VB, for example using Visual Studio, firstly it is necessary to create the user interface and then code the predetermined events using the premade objects, which are named controls, and are accessible on the toolbar of Visual Studio.⁷⁰ By selecting a type of form, for example a Windows form, which is used for the development of Windows native applications, a blank page is shown. The developer can then insert various objects on this page in order to create the user interface, as demonstrated on appendix 3.⁷⁰

The main controls used for VB, as stated below, are shown on appendixes 4 to 11:^{69,70}

- Button, a squared object which triggers a consequence when clicked by the user;
- Combo box, which gives a list of text options where the user has to choose an option from the list;
- Group box, used to group objects;
- Label, used to insert text that is not changeable by the user;
- Link label, a label with an embed link, which triggers a consequence when clicked by the user;
- Radio button, which is used when several options are available, and the user can select one;
- Tab control, used to divide the objects into different tabs;
- Text box, which permits the user to observe outputs of text or to insert/edit text;

After inserting an object, it is possible to double click it to be redirected to the code page, in which the code regarding that object will be written. An example of the code page can be consulted on appendix 12.⁷⁰

3. Methods

The development of this study can be divided in three phases. The first phase consisted on obtaining a fair amount of information to build a database that fairly represented the current practices in oncology treatments and disease management for localized prostate cancer.

On the second phase, the interface itself was built, so that the knowledge base was digitally integrated in a way that it could communicate with the user and in order to generate outputs after predetermined information is inserted in the system.

On the last phase, clinical case reports described on the literature were applied to OnCATs in order to test the system's workflow and confirm its conditions of applicability.

The illustrations presented on this study were developed recurring to Lucidchart mobile app.⁷¹

3.1 Knowledge base construction

To start building the knowledge base, a web search was conducted, including the keywords "prostate cancer", "treatment", "management" and "guidelines". This search led us to obtain a total of 13 published guidelines of worldwide well-known professional associations and committees.^{9,10,37-39,11-17,23}

Using these guidelines as a baseline reference, it was important to take note of relevant information and criteria that would allow the definition of an algorithm to assess the optimal treatment course(s) and treatment protocol(s). While analyzing the obtained data, it was explicit that information in some areas regarding radiation oncology, such as stereotactic treatments and brachytherapy, was somewhat scarce. In order to bridge this gap, a second web search using the keywords "prostate cancer", "stereotactic body radiotherapy" and "guidelines" was conducted.^{59,72-74} Following that, a third web search was conducted using the key-words "brachytherapy", "prostate cancer" and "guidelines".^{18,19,53,75-77}

At the end, after reviewing the guidelines obtained from all three web searches, we ended up with a total of 23 published guidelines to incorporate on the OnCATs original knowledge base. Guidelines published by the following associations and entities, 22 in total, were included in this study:

- Alberta Health Services, Canada;¹⁷
- American Association of Physicists in Medicine (AAPM), United States of America (USA);^{59,73}
- American Brachytherapy Society (ABS), USA;^{18,19,76}
- American College of Radiology (ACR), USA;^{10,74,76}
- American Society for Radiation Oncology (ASTRO), USA;^{11,37,74}

- American Society of Clinical Oncology (ASCO), USA;^{37,75}
- American Urological Association (AUA), USA;^{11,37}
- Cancer Care Ontario (CCO), Canada;⁷⁵
- European Association of Urology (EAU), Europe;¹³
- European Organization for Research and Treatment of Cancer (EORTC), Europe;³⁸
- European Society for Medical Oncology (ESMO), Europe;¹²
- European Society of Radiotherapy (ESTRO), Europe;^{13,39}
- European Society of Urogenital Radiology (ESUR), Europe;¹³
- International Society of Geriatric Oncology (SIOG), Global;¹³
- International Society or Urological Pathology (ISUP), Global;^{78,79}
- Nacional Clinical Effectiveness Committee (NCCEC), United Kingdom;¹⁴
- National Comprehensive Cancer Network (NCCN), USA;⁹
- National Health Service (NHS), United Kingdom;¹⁵
- National Institute for Health and Care Excellence (NICE), United Kingdom;^{16,77}
- Radiosurgery Society (RSS), United States of America;⁵⁹
- Royal Australia and New Zealand College of Radiologists (RANZCR), Australia and New Zealand;⁷²
- Society of Urological Oncology (SUO), USA;¹¹

The organization of the obtained information in the predetermined categories was proven to be crucial to define the applicability of each data group within OnCATs' workflow. The information was stored in tables using Microsoft Excel by the following criteria:

- Risk classification definition;
- Treatment course assessment;
- RT dose prescription;
- ADT dose prescription.

The goal was that the data was to be organized in a way that was as close as possible to the workflow in which prostate cancers are submitted to when a healthcare team is analyzing the available courses of action. By following this organization method, it was easier to know which kind of information was needed to be retrieved by the algorithm on the different phases of the OnCATs workflow.

3.2 System design

Having the knowledge base ready to be put to practice, the next step was to build an interface that allows the communication between the user and the knowledge base, and also the accommodation of results output.

The interface was built in the form of a computerized software, meant to be used on the Microsoft Windows operating system. The software was developed using Microsoft Visual Studio 2010, which is an Integrated Development Environment (IDE), developed by Microsoft Corporation, for the development of computer software, websites and mobile apps.⁷⁰ A representation of OnCATs conceptual model can be consulted bellow, on figure 1.

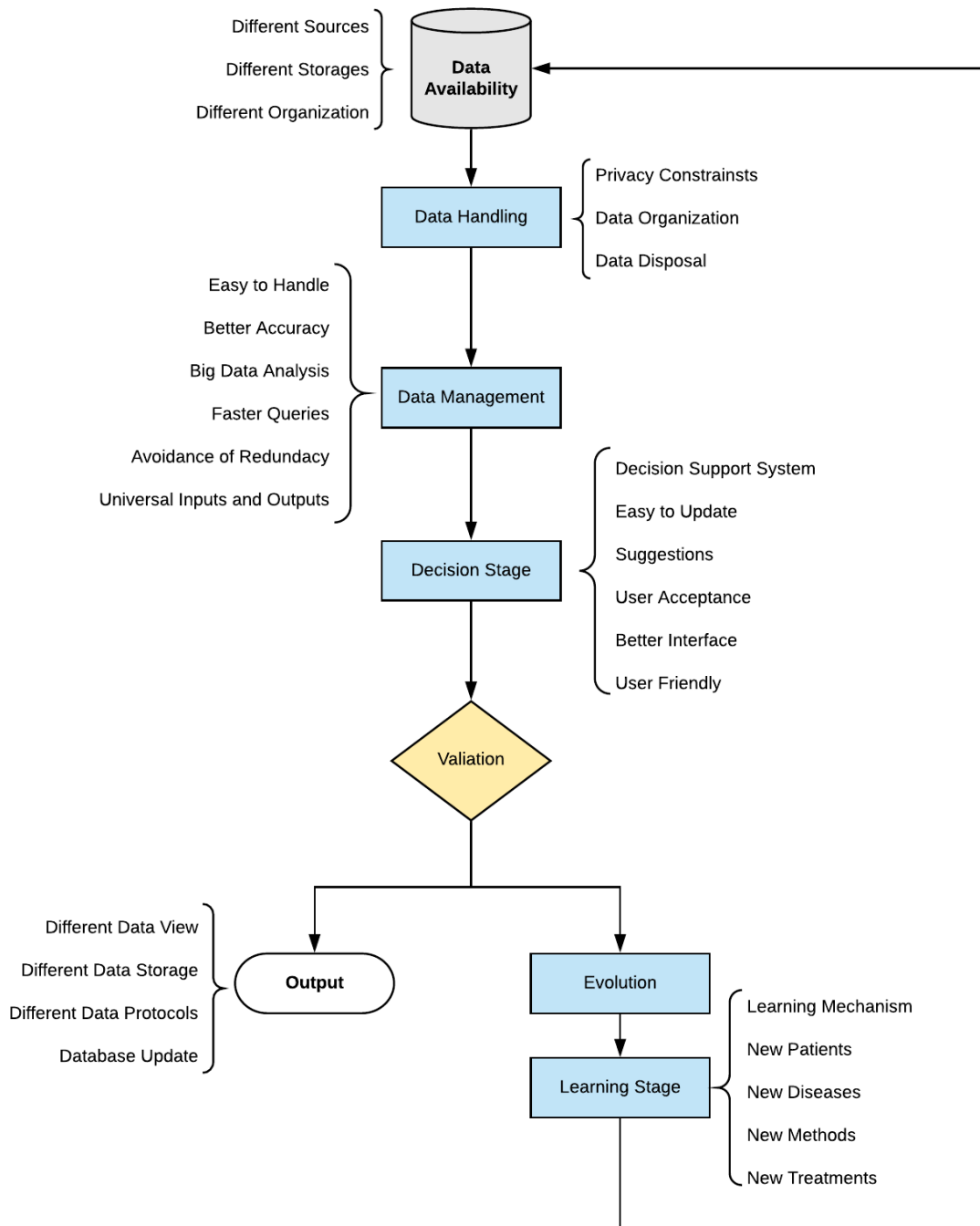


Figure 1 - Conceptual model of the development of OnCATs, represented in a fluxogram.

For the development of OnCATs, the first step was to create a new project within Visual Studio. A Windows Form Application was used, which means this clinical DSS will be intended to be executed on computers running Windows operating system. Using the toolbox available on Visual Studio, a tab control was applied in order to separate the clinical DSS into the following categories of interest:

- “Login Page”;
- “Home Page”;
- “New Patient”;
- “Treatment Course Assessment”;
- “Treatment Prescription”;
- “Report”.

The mentioned categories are representative of the OnCATs workflow, which itself is based on the workflow that healthcare professionals use for prostate cancer treatment and assessment. After building the specific pages (tabs) for all stages of the OnCATs workflow, the available controls on the toolbox were used to build an interactive system that facilitates the addition and exportation of information. Text boxes were used for simple text input and output, control boxes were used for when multiple options for one category were available, buttons were used for simple “yes” or “no” questions or to execute commands, and radio buttons were used to choose between a list of outputs. Labels, link labels and group boxes were also used for descriptions, organization and aesthetics.

Throughout all the system’s workflow, security measures, such as pop alerts and double-verification obligatory requirements are applied, to stimulate the user to confirm all the inserted data at least twice. This allows the avoidance of errors by omission or misplacing of information. Other security measures were also applied to warn the user if the system was not being properly used for any reason, and as well to give indication of any capabilities of the system that are not present or are under development, such as the ability to use OnCATs on metastatic disease patients or on prostate tumors different than adenocarcinomas.

Throughout all phases of the OnCATs workflow, on the bottom of each page, is located a text box in which are displayed the references in which the showed protocol or course of action is based. This measure was placed so users could check in real-time the veracity of the data that is presented to them. If for any reason the user does not agree with the information presented, means are available for users to insert new data based on their judgement an experience. If external data is added to OnCATs by the user, on the references text box will be displayed that the shown information was inserted by that specific user on the date it was submitted.

3.3 System workflow

A summary of the workflow of the OnCATs algorithm can be consulted on the fluxogram represented on figure 2. The first stage of the OnCATS workflow is to verify to which risk group a specific patient belongs to.⁹ After the user inserts the information on the system regarding

the tumor stage, GS and PSA level, the system will then assign the patient one of the following risk groups, based on the criteria represented on table 1.^{9,10,19,11-18}

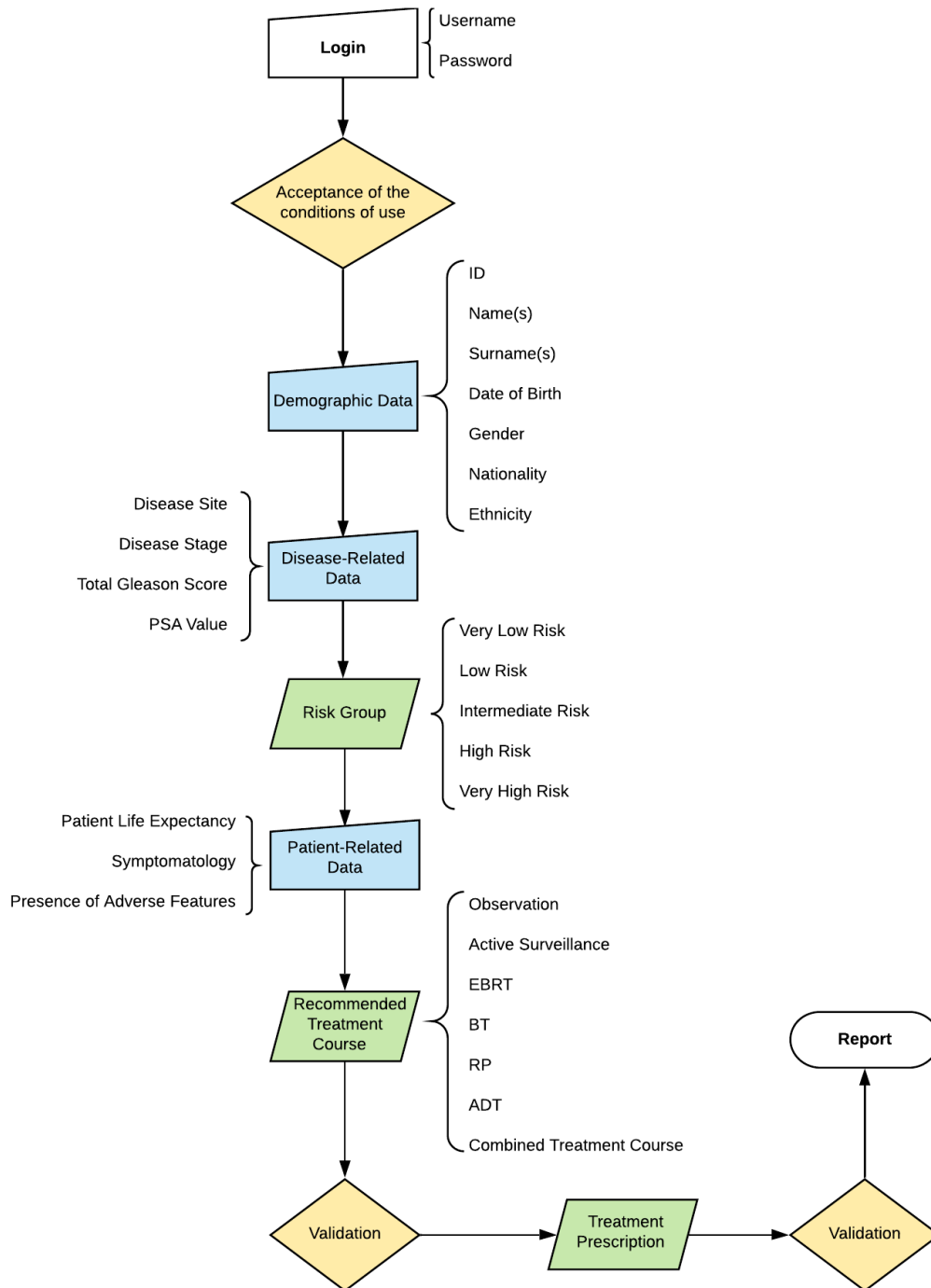


Figure 2 - Representation of the OnCATs' clinical workflow.

Table 1 - Criteria for risk assessment for prostate cancer, based on clinical features.

Risk Group	Tumor Stage			Gleason Score	PSA (ng/ml)
	T	N	M		
Very Low	1c	0	0	< 7	< 10

Low	1 - 2b	0	0	< 7	< 10
Intermediate	< 3a	0	0	7	< 20
				< 7	10 - 20
High	3a	0	0	8 - 9	< 20
				< 8	> 20
Very High	≤ 4	0	0	10	Any
Regional Disease	Any	1	0	Any	Any
Metastatic Disease	Any	Any	1	Any	Any

The second stage of the workflow is to assess the available treatment options. By evaluating the patient's estimated life expectancy, presence of symptoms and presence of adverse tumor features, the system will recommend at least one of the following treatment courses:

- Radical Observation;
- Radical AS;
- Radical ADT;
- Radical BT;
- Radical EBRT;
- EBRT with ADT;
- EBRT with adjuvant BT;
- EBRT with adjuvant BT and ADT;
- RP;
- RP with adjuvant EBRT;
- RP with adjuvant EBRT and ADT;
- RP with adjuvant Observation;
- RP with PLND and ADT;
- RP with PLND and adjuvant Observation;
- RP with PLND and adjuvant EBRT and ADT.

The criteria for treatment course assessment for prostate cancer patients with localized disease can be consulted on table 2.^{8,9,23,35,37-39,10-17} Since choosing between different treatment modalities can be challenging, recommendations of applicability for each treatment modality do exist and serve as support for deciding the appropriate treatment course for a given patient. An example of conditions of applicability for prostate cancer treatments can be consulted on table 3.^{9,11,75,76,13-19,53}

Table 2 - Criteria for assessment of treatment course for localized prostate cancer patients, by risk group.

Treatment Course Assessment Criteria					
Patient and Disease Characteristics			Risk Group		
Life Expectancy (Years)	Symptomatology	Presence of Adverse Features	Very Low and Low Risk	Intermediate Risk	High and Very High Risk
< 6	Asymptomatic	Present or Not Present	No workup until the disease becomes symptomatic	No workup until the disease becomes symptomatic	Observation ADT EBRT
	Symptomatic	Not Present	Observation	Observation EBRT BT	EBRT + ADT EBRT + BT.+ ADT RP + PLND
		Present	Observation	Observation EBRT + ADT EBRT + BT + ADT BT	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation
6 - 9	Asymptomatic	Not Present	Observation	Observation EBRT BT	EBRT + ADT EBRT + BT.+ ADT RP + PLND
		Present	Observation	Observation EBRT + ADT EBRT + BT + ADT BT	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation

(Continues on next page)

Patient and Disease Characteristics			Risk Group		
Life Expectancy (Years)	Symptomatology	Presence of Adverse Features	Very Low and Low Risk	Intermediate Risk	High and Very High Risk
> 9	Asymptomatic or Symptomatic	Not Present	AS EBRT BT RP	AS BT EBRT RP RP+PLND	EBRT + ADT EBRT + BT.+ ADT RP + PLND
		Present	AS EBRT BT RP + EBRT RP + EBRT + ADT RP + Observation	AS BT EBRT + ADT EBRT + BT EBRT + BT + ADT RP + EBRT + ADT RP + Observation RP + PLND + EBRT + ADT RP + PLND + Observation	EBRT + ADT EBRT + BT + ADT RP + PLND + ADT RP + PLND + EBRT + ADT RP + PLND + Observation

Table 3 - Recommended criteria for treatment modality selection.

Active Surveillance	Brachytherapy	External Beam Radiotherapy	Observation	Radical Prostatectomy
Younger patient	No previous TURP performed	Patient has not been submitted to prior pelvic irradiation	Elder patient	No contraindications for surgical procedure
Seemingly painless disease	Acceptable operative risk	No active inflammatory disease of the rectum	Patient with comorbidities	Clinically localized tumor
Asymptomatic disease	No bladder outlet obstruction	No permanent indwelling Foley Catheter	Asymptomatic disease	Life expectancy superior to 9 years
Patient refuses curative treatment	Total prostate volume inferior to 50 cm ³	No obstructive and non-cancerous related lower urinary function		Tumor is not fixed to the pelvic wall
	Severe urinary symptoms not present			No invasion of urethral sphincter

In third stage of the workflow, the system assists the prescription of each individual treatment modalities that are part of the chosen treatment course. It is important to note that each different treatment modality has different prescription criteria, due to their different natures and goals. The prescription of Observation and AS follow the criteria demonstrated on table 4.^{9,11,13,14,16,17}

Table 4 - Recommended treatment protocols for AS and Observation.

Active Surveillance	Observation
mpMRI every 12 months	PSA test every 6 months
PSA test every 3 – 6 months	Physical exam every 6 months
DRE every 6 months	
Biopsy every 6 months	

As for ADT, the different approaches are represented on figure 3.^{9,13,77} All the mentioned ADT approaches were included on the OnCATs workflow, due to their clinical relevance.

As for the treatment duration, this parameter is independent from the type of ADT chosen, but is highly dependent of the patient’s risk group and chosen treatment course. A summary of the treatment duration of ADT regimens by risk group and treatment course can be consulted on figure 4.^{9,13,16} If a surgical approach, such as bilateral orchidectomy, is preferred, the treatment duration is permanent. Since in this procedure the testicles are surgically removed, the treatment is therefore irreversible.

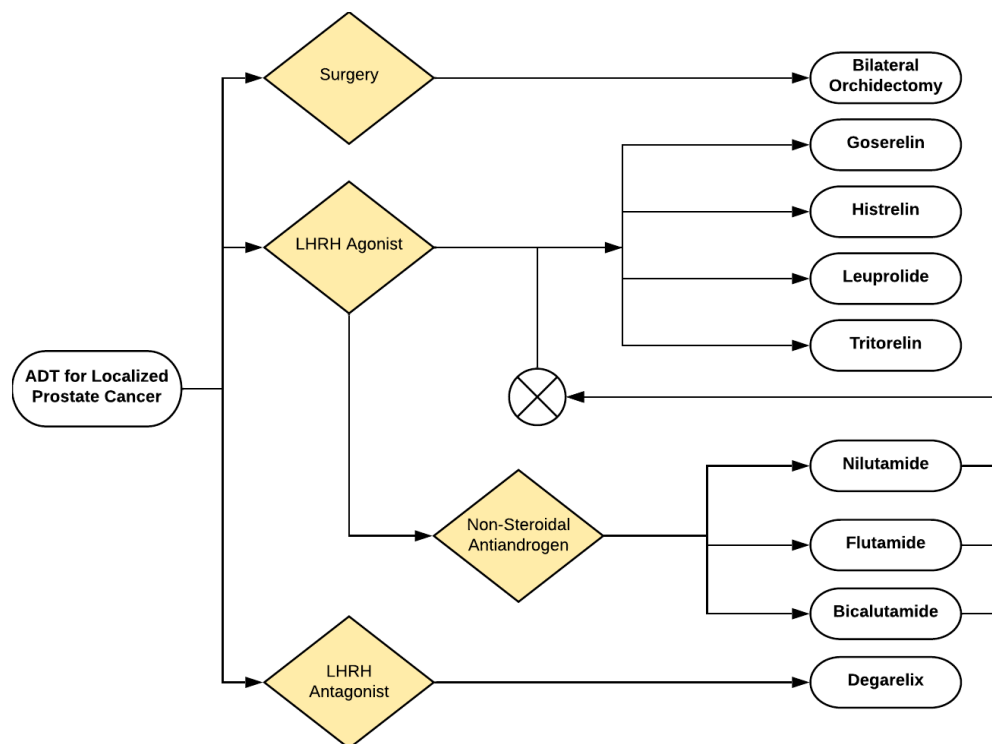


Figure 3 - Representation of the different ADT approaches for localized prostate cancer.

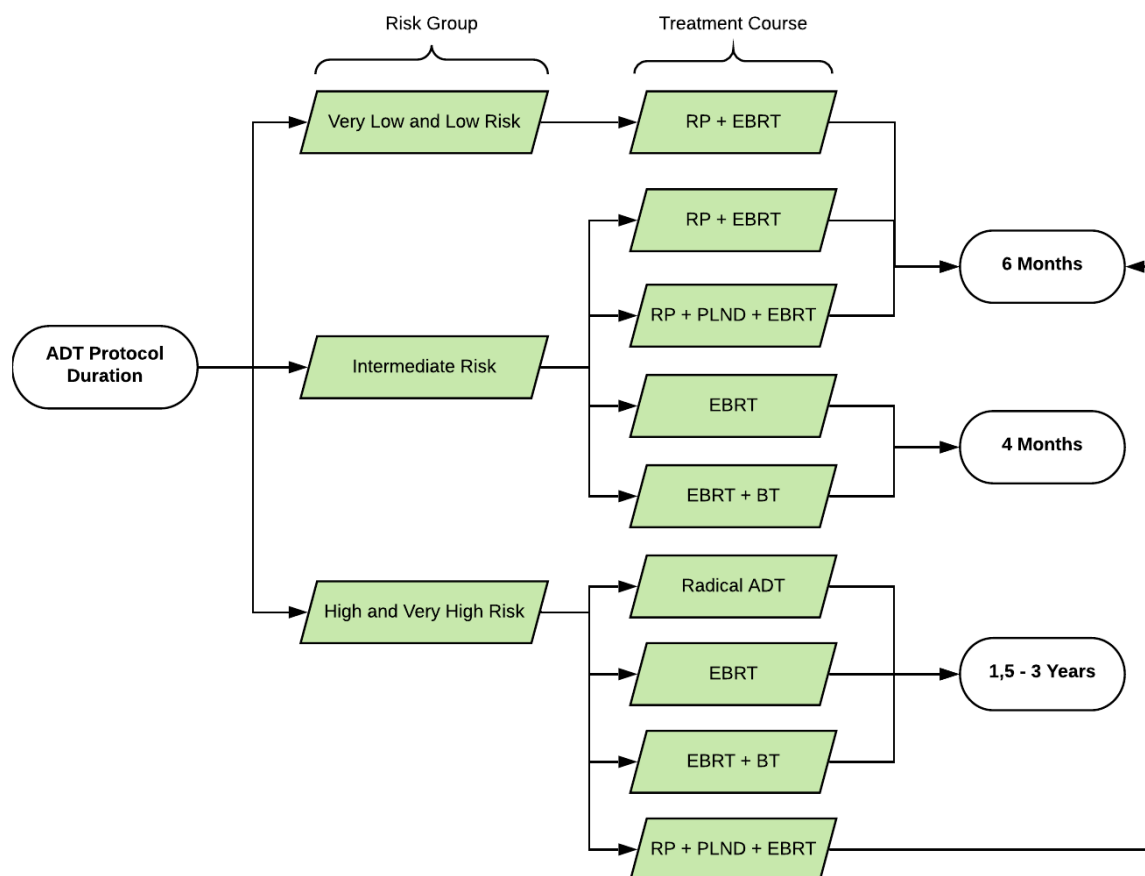


Figure 4 - Treatment duration for non-surgical ADT options by risk group and elective treatment option.

As for EBRT, the dose prescription is highly dependent from the type of fractionation applied. During this stage, it is important to note that extreme hypofractionated regimens are only safe to be delivered with stereotactic techniques. The dose prescription for Radical EBRT follows the criteria demonstrated on figure 5.^{9,10,13,16,17,37}

EBRT can also be delivered in combination with other therapies. As described on table 2, BT can be applied as a boost after primary EBRT. For this combined treatment course, it is important to evaluate which kind of BT, LDR or HDR, and which radioactive isotope is to be used, as this greatly impacts the value of the total prescribed dose. The dose prescription of adjuvant BT after EBRT follows the criteria on figure 6.^{9,13,17-19,76} The same chain of thought is applied to the dose prescription of radical BT. The dose prescription for radical BT follows the criteria on displayed on figure 7.^{9,18,76}

Besides that, EBRT can also be delivered after RP. Guidelines recommend that adjuvant EBRT after RP is delivered in conventional fractionation, so highly conformal techniques such as 3DCRT, IMRT or VMAT are preferred. The dose prescription of adjuvant EBRT after RP follows the criteria on figure 8.⁹

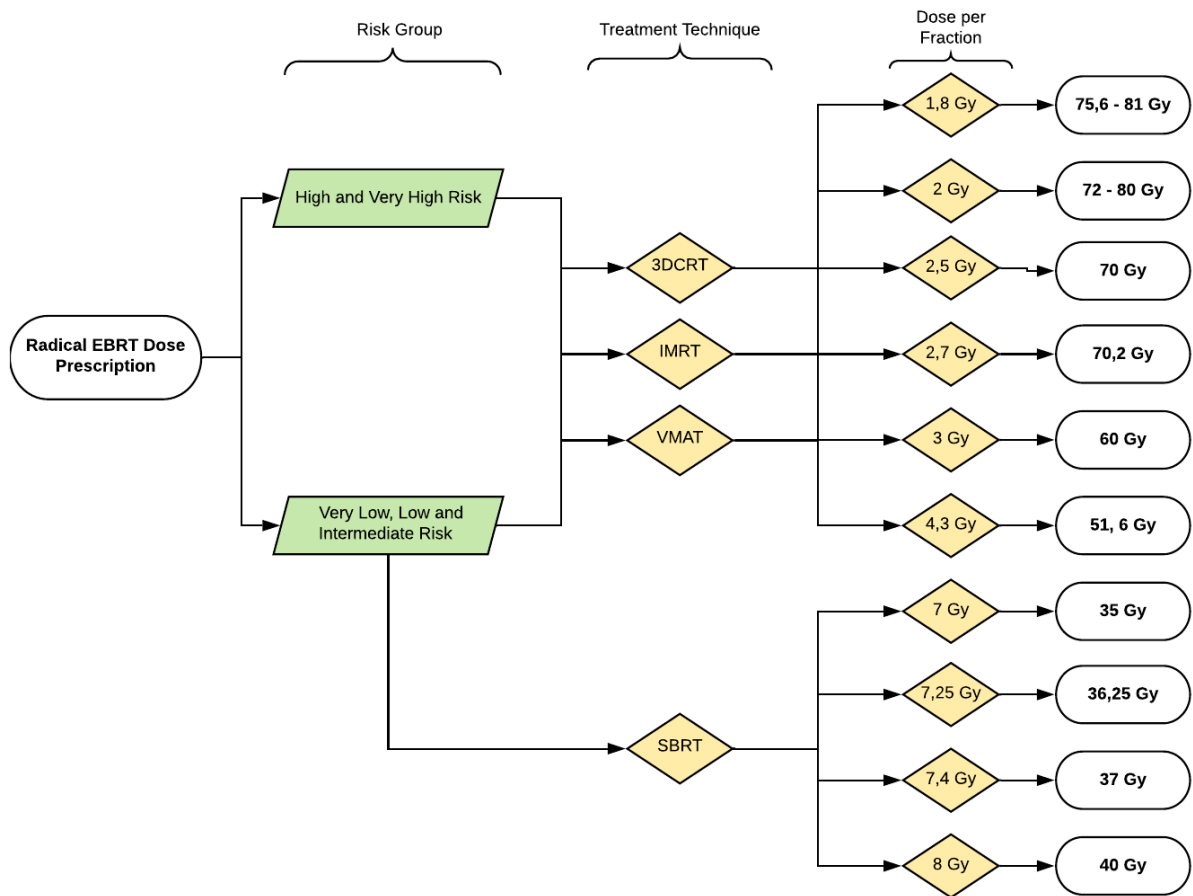


Figure 5 - Representation of the total dose prescription for primary EBRT for prostate cancer.

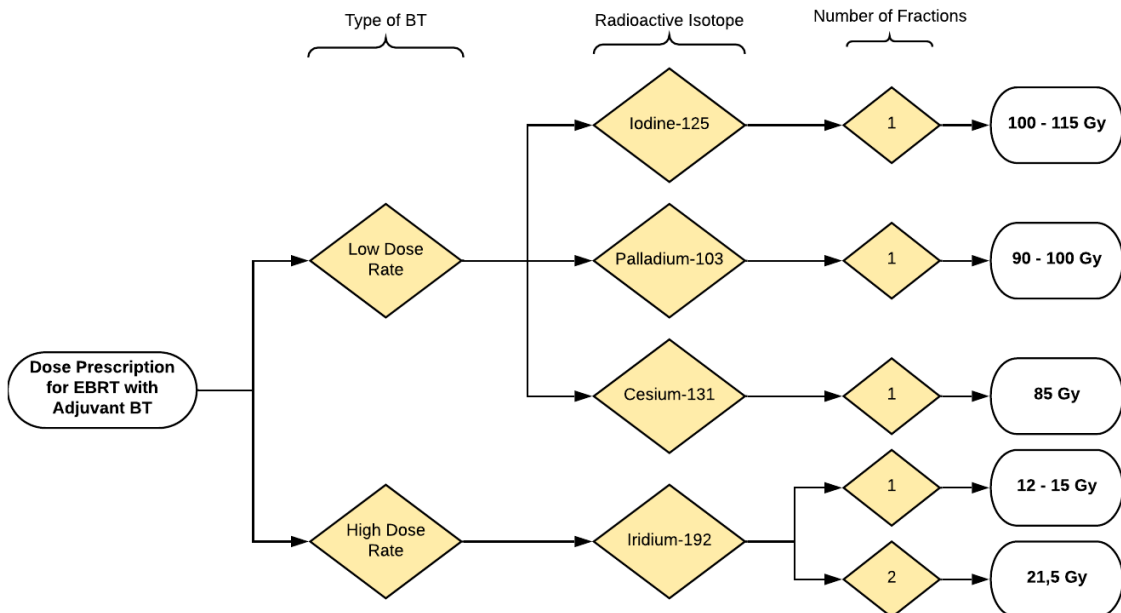


Figure 6 - Representation of the total dose prescription for primary BT for prostate cancer, applicable to intermediate, high and very high patients.

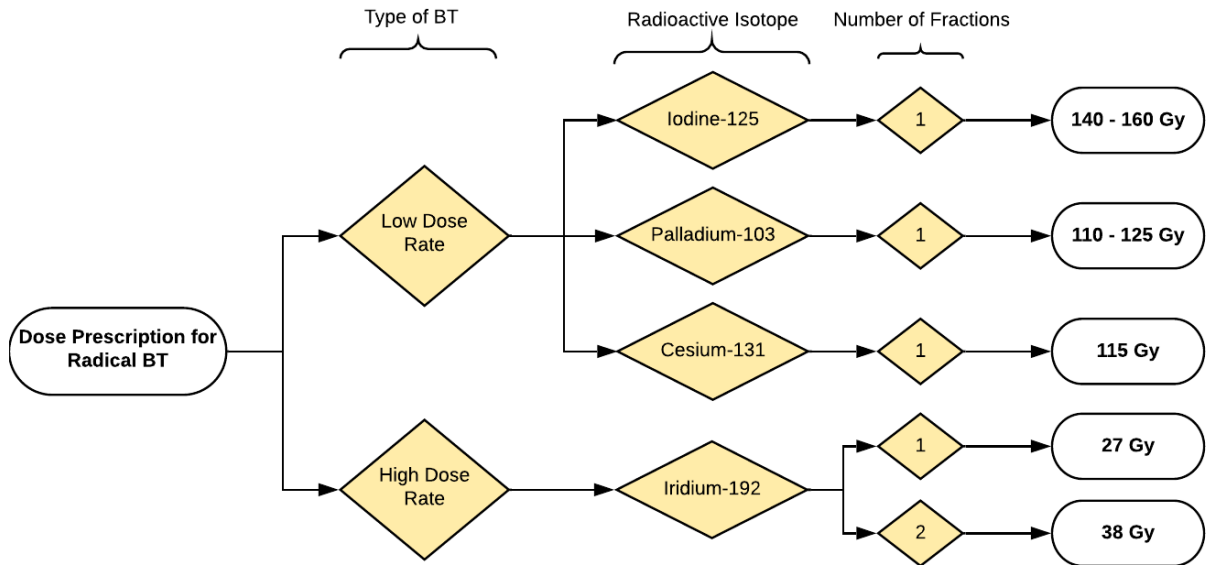


Figure 7 - Representation of the total dose prescription for primary BT for prostate cancer, applicable to very low, low and intermediate risk patients.

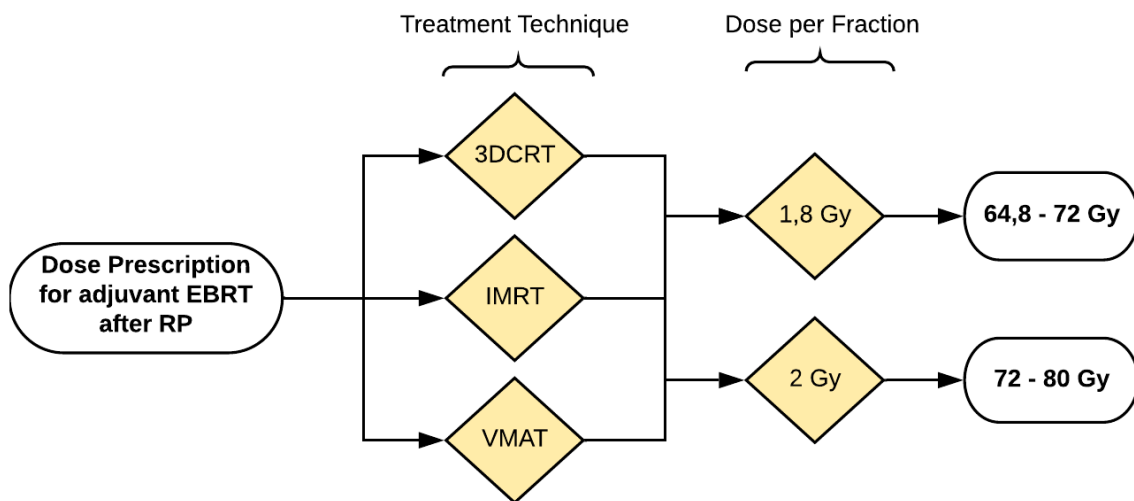


Figure 8 - Representation of the total dose prescription for adjuvant EBRT after RP, applicable to all risk groups.

3.4 System testing

In order to evaluate if the OnCATs workflow could successfully simulate the clinical workflow for prostate cancer treatments, clinical cases of real patients were necessary. To obtain these cases, we resorted to the Journal of Medical Case Reports website, where a web search was conducted using the keywords “prostate” and “cancer”.⁸⁰ After consulting the list of shown publications, articles that did not contain the word “prostate” in its title, or were reports of patients with regional or metastatic disease, were excluded. To complement these results, another web search was conducted on the platform PubMed.⁸¹ Using the advanced search function, we searched for articles that contained the words “prostate” and “cancer” in its title, but did not contain the words “metastatic” or “metastasis”. Filters were applied in order to display only case reports, articles with full text available for free, published in last 5 years, and written in English. The same inclusion and exclusion criteria were applied on both web searches. After revising all the publications, a total of 10 clinical cases were obtained.

The method of Kim *et al.* was applied to estimate the patients’ life expectancy.³² Regarding the quartile of health, we considered patients who had comorbidities, such as *diabetes mellitus* or hypertension, to not be healthy, and therefore were placed on the bottom quartile of health (bottom 25%). On the other hand, patients who did not have other comorbidities, we considered to be very healthy, and therefore were placed on the top quartile of health (top 25%). For the cases in which there was no mention of the presence of comorbidities, we assumed that they were overall healthy and therefore were placed on the middle quartile of health (between 25 – 75%). On real case scenario, these estimates may not be accurate, and should instead be the result of careful and specific assessment by a physician.³²

As for the presence of symptoms, for the clinical cases where there was no indication if the patient was symptomatic or not, since prostate cancer tends to only manifest its symptoms when the tumor is in higher stages, we assumed the patients on lower stages were asymptomatic at the time of diagnosis, while patients on higher stages were symptomatic.²⁸

For defining the presence of adverse features, the criteria described on chapter 2.2 should be applied. For clinical cases where there was no mention on case report if adverse features were present, we assumed the absence of any of these features.

After analyzing and compiling the information regarding these clinical cases, we aimed to recreate the assessment and treatment prescription process using OnCATs, in order to evaluate if a physician’s logic and process of thought could be replicated by the system. A pass/fail analysis was performed, where it was assessed if the system was able to suggest the option that constituted the real course of action of that given patient (pass), or suggested options different than what constituted the real course of action of that action (failed).

4. Results

Firstly, as result of this research, it is relevant to demonstrate how OnCATs was developed, how the algorithm works, and what measures were taken into account in order to assimilate its workflow with the real workflow for cancer treatment. As mentioned on chapter 3.2, OnCATs was developed in several phases, which need to be followed in succession to obtain a fully detailed clinical report regarding the medical assessment of a specific patient.

4.1 Login page

When the system is booted, the first page that is presented to the user is the Login page, as shown on figure 9. In this page, the user has to insert on the two present text boxes a valid combination of username and password, in order to be able to access the system.

This combination needs to be previously determined, by allowing the system to recognize a sequence of characters as a valid text input on both the Username text box and the Password text box, using an if-then condition. This measure was placed for security reasons, as we only intend to allow authorized users to access this system, due to the nature of the data being processed and exported. The user's username will be displayed on the following pages of the OnCAT's workflow. If by any instance a wrong combination of username and/or password is put, a pop-up alert emerges, asking the user to insert valid credentials. When a valid combination of username and password is put, the user is transported to the next page.

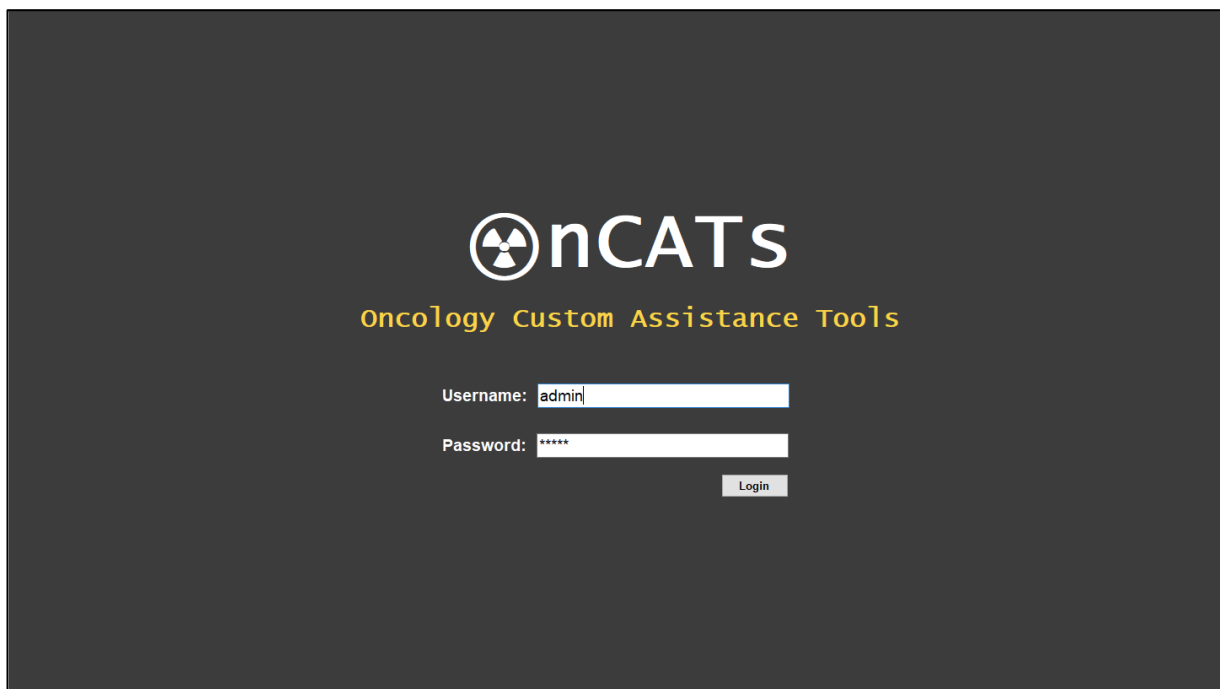


Figure 9 - Representation of the Login page of the OnCATs DCSS.

4.2 Home page

After login, the user is presented with the “Home Page”. On this page, the user will be confronted with a legal disclaimer. The disclaimer, cited below, was placed to disclaim any possible liabilities that may arise due to output errors generated by OnCATs, while also giving extra instructions on how to properly use the system:

“This assistance tool was developed for research purposes only. It does not constitute a substitution for medical assessment and should only be used as reference assistance tool on medical oncology disease management. The reports generated by this software should always be validated and signed by a licensed medical professional. The information displayed is based on clinical guidelines and clinically relevant researches, published by reference corporations and multidisciplinary professional associations. We disclaim any liability for errors, omissions or misinformation. For any additional information, please contact us via the contact information displayed below. By clicking on Start, you are agreeing with these conditions.”

A representation of the OnCATs’ “Home Page” and legal disclaimer can be consulted on appendix 13. By accepting these conditions and clicking on the “Start” button, the user agrees to the terms of use of OnCATs and is transported to the next page.

4.3 Inserting a new patient

After logging in and accepting the system’s conditions of use, the “New Patient” tab is presented. This is the first page in which the user starts the decision-making process, by firstly inserting information regarding the patient.

Initially, only demographic data, including patient ID, names and surnames, date of birth, gender, among other information, is requested. This personal data is important for identifying the patient on the final report. It is also useful for availability of data for clinical trials and sorting of patients in groups, making it possible to evaluate in the future any new variables that may play a bigger role on the algorithm’s functionalities. Optionally, a picture of the patient can also be uploaded, as an extra security measure for avoiding mixing up similar reports.

After filling all the personal data requested by the system, the system asks the user to confirm if all the inserted data is correct.

If the user validates all the information, by clicking on the “Yes” button, a new set of text boxes and combo boxes, which are related to assessing the risk group, are displayed to the user below on a group box. On the other hand, if the user finds that any of the listed information is not correct, by clicking on the “No” button, all information is erased and the user has a new chance to re-insert correctly all the required information.

4.3.1 Risk group assessment

The process of risk group assessment starts with the user informing the system which kind of cancer we are aiming to treat, by defining the disease site on the correspondent combo box. Despite several options being available on this combo box, if an option other than “Prostate” is chosen, a pop-up alert emerges to inform the user that, for the moment, OnCATs can only be applied to prostate cancers. If “Prostate” is promptly chosen, another pop-up alert emerges to inform the user that OnCATs can only be applied to prostate tumors which are histologically adenocarcinomas, which presets the tumor’s histology.

After choosing a valid disease site, the process of assigning the risk group immediately starts. On a new set of combo boxes, which are displayed to the user in succession, it is necessary to assign a grade to each TNM system categories for tumor staging, in addition to the GS and PSA value at the time of assessment. During this process, while the user selects a grade for T, N and M grades, on a text box located laterally, the TNM grading definition by the AJCC is displayed in real time. On the combo boxes regarding the N and M grading, if other grades different than 0 are chosen, for either of these variables, a pop-up alert is shown to inform the user that, at the moment, OnCATs can only be applied to localized prostate tumors. After informing the system of the tumor stage, while assigning a total GS, the grading definition by the ISUP consensus is also displayed in real time on the same text box. This measure was placed so users could have a practical sense of what those grades clinically represent.^{9,22,79}

After inserting a valid tumor stage, GS and PSA, by pressing the “Calculate” button, the system’s algorithm will be able to successfully characterize the patient into a risk group, based on the NCCN nomenclature, as shown on figure 10.⁹

Lastly, for the normal workflow of the system to continue, the user has to confirm that all inserted and displayed information is correct. If for any reason any of the inserted data is not correct, the user has the chance to manually correct it and ask the system to perform a new calculation.

Having assigned a risk group to the patient, it is time for the evaluation of the treatment options available for that patient.

OnCATs Risk Assessment | Home | Logged in as: admin

Demographic Data ✓

Patient ID:


Surname(s): Name(s):

Nationality: Ethnicity:

Date of Birth: Age: years

Gender:

Patient Picture



[Change](#)

Risk Group Assessment

Disease Site: Histology:

Clinical Stage:

Total Gleason Score: ISUP Consensus Grade:

PSA Value: mg/ml

Risk Classification: **Intermediate Risk**

Do you confirm this information is correct?

Description by the AJCC and ISUP Consensus:

T Grade:
- Tumor is palpable and confined within prostate, involving more than one-half of one side but not both sides.

N Grade:
- No positive regional lymph nodes.

M Grade:
- No distant metastasis present.

Gleason Score Description:
- Only individual discrete well-formed glands.

Prostate Specific Antigen Description:
- The patient's blood has a concentration of prostate-specific antigen between 10 ng/mL.

References

Risk Group Assessment:

- American Joint Commission on Cancer. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
- Epstein JI, Allsbrook WC, Amin MB, Egevad LL, Bastacky S, López Beltrán A, et al. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. Am J Surg Pathol [Internet]. 2005;29(9):1228–42. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16096414>
- (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from:

Figure 10 - Representation of the “New Patient” tab on OnCATs DCSS after the user fills all the information and an output response is generated.

4.4 Assessing the treatment course

Following the risk assessment, on the “Treatment Course Assessment” tab, the first information the user has to fill in is the patient life expectancy. There are three available options on the correspondent combo box: inferior to 6 years (< 6 years), between 6 to 9 years (6 – 9 years) and greater than 9 years (> 9 years), which the user might choose based on the assessment and evaluation of the patient.

There is although a fourth option, which allows the user to assess in real time an estimate of the patient’s life expectancy. By selecting the “Calculate” item on the life expectancy combo box, the user is redirected to the online calculator for assessment of the estimate patient life expectancy, developed by Kim *et al.*, as demonstrated on appendix 14.^{32,82} This constitutes an option for when the users have no other way of estimating the life expectancy of a patient.

For the last two steps regarding the treatment course assessment, the user has to select on two combo boxes if the patient is symptomatic and if the tumor displays any kind of adverse features.

By combining the estimated life expectancy, symptomatology and presence of adverse features, OnCATs can recommend one, and if possible, more than one, treatment course(s) for that patient. These available treatment courses are displayed on a list, and the user has to choose one option by selecting the corresponding radio button. When a treatment option is selected by the user, the recommendations of applicability, represented on table 3, are displayed in real-time on a text box located laterally, as a measure to assist the decision when multiple options are available. On figure 11 it is possible to consult a visual representation of the “Treatment Course Assessment” tab of the OnCATs system.

If it happens that the user does not agree with any of the recommended treatment courses, it is possible to insert a new line with blank text boxes, in which the user is able to insert a different treatment course consisting of up to 4 different treatment modalities.

Once again, for the normal workflow of the system to continue, the user has to confirm that all inserted and displayed information is correct.

OnCATs Treatment Access | Home | [Risk Assessment](#) | Logged in as: admin

Patient Information

ID:

Disease Site:

Risk Classification:

Treatment Course Assessment

Patient Life Expectancy: years

Is this patient symptomatic? Does the tumor have adverse features?

Recommended Treatment: Choose one of the recommended therapeutic schemes or click [here](#) to insert a new one.

Active Surveillance
 BT
 EBRT + ADT
 EBRT + BT
 EBRT + BT + ADT
 RP + EBRT + ADT
 RP + Observation
 RP + PLND + EBRT + ADT
 RP + PLND + Observation

Do you confirm this information is correct?

References

Therapeutic Scheme:

- (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54, 57–61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- Committee National Clinical Effectiveness. Diagnosis, staging and treatment of patients with prostate cancer National Clinical Effectiveness Committee [Internet]. 2015 [cited 2019 Dec 5]. Available from: <http://www.hse.ie/eng/services/list/5/cancer/proinfo/guidelines/prostate/prostateguideline.pdf>

Treatment Requirements

Brachytherapy (BT):

- No previous Transurethral Ressection of the Prostate (TURP);
- Acceptable operative risk;
- No bladder outlet obstruction;
- No severe urinary symptoms.
- Total prostate volume inferior to 50 cc.

External Beam Radiotherapy (EBRT):

- Patient has not be previously subdoe to pelvic irradiation;
- No active inflammatory disease of the rectum;
- No permanent indwelling Foley catheter;
- No obstructive cancer related lower urinary function.

Figure 11 - Representation of the “Treatment Course Assessment” tab on OnCATs DCSS after the user fills all the information and an output response is generated.

4.5 Prescribing a treatment

Having decided the optimal treatment course, the next stage on the OnCATs workflow is to individually prescribe each treatment modality that is part of the decided treatment course. Because of that, the “Treatment Prescription” tab is divided in subtabs. In each subtab is represented one the different treatment courses mentioned on chapter 3.3. The treatment course that the user chooses on the “Treatment Course Assessment” tab decides which subtab is presented to the user, and all the prescription process happens on that displayed page.

When the chosen treatment course is constituted by more than one different treatment modality, the prescription of each treatment modality happens in successive phases.

4.5.1 Observation

For prescribing an Observation protocol, as stated in chapter 2.3.1, patients should undergo a protocol consisted by periodical examining, including PSA tests and physical exams, such as DRE.^{11,13,14,16,17}

When the Observation page is presented to the user, a treatment protocol, based on the information stated on table 4, is displayed as a starting point. Figure 12 shows the workflow for the prescription of radical Observation using OnCATs. The user has then the option to accept the shown protocol or to refuse it, by either clicking on the “Yes” or “No” buttons respectively. If the protocol is refused, the information displayed on the text boxes is erased and a pop-up alert emerges to inform the user that new valid data should be inserted, in order to progress. Either way, after a successful validated Observation protocol is defined, the user is directed to the report page.

4.5.2 Active surveillance

Similar to the prescription of Observation, for AS, an AS protocol, based on the information stated on table 4, is displayed to the user. On figure 13 is demonstrated the workflow for the prescription of radical AS using OnCATs. The shown protocol can also either be accepted or refused. If refused, the information on the text boxes is erased and a pop-up alert emerges to inform the user that new valid data should be inserted, in order for the user to be able to progress. Either way, after a successful AS protocol is defined and validated, the user is taken to the report page. Laterally on this page, are also shown recommendations for the different MRI parameters for the mpMRI acquisition, which are the most indicated for AS protocols intended for prostate cancer patients. The parameters for mpMRI acquisition should be the same as discussed on chapter 2.3.2.

ncATS Prescription | Home | Risk Assessment | Treatment Access | Logged in as: admin

Patient Information

ID: 13213123 Treatment Course: Observation

Disease Site: Prostate

Risk Classification: Intermediate Risk

Observation Protocol

PSA Blood Test: Performed at day 1 and then every 6 months.

Digital Rectal Exam: Performed at day 1 and then every 6 months.

Protocol Duration: Until patient becomes symptomatic or imminently symptomatic

Adjuvant Treatment(s): Palliative ADT

Do you confirm this information is correct?

References

Observation Protocol
 • (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Figure 12 - Demonstration of OnCATs' Observation tab for the prescription of radical Observation.

OnCATs Prescription | Home | Risk Assessment | Treatment Access | Logged in as: admin

Patient Information

ID: 23233 Treatment Course: Active Surveillance

Disease Site: Prostate

Risk Classification: Intermediate Risk

Active Surveillance Protocol

Multi-Parametric MRI: Performed at day 1 and then every 12 months.

PSA Exam: Performed at day 1 and then every 6 months.

Digital Rectal Exam: Performed at day 1 and then every 12 months.

Prostate Biopsy: Performed at day 1 and then every 12 months.

Protocol Duration: Until tumor progression occurs

Adjuvant Treatment: Curative Treatment

Do you confirm this information is correct?

Recommendations

Multiparametric MRI (mpMRI):

- Anatomical T2-Weighted Image
- Diffusion Weighted Image
- Dynamic Contrast-Enhanced Image

References

Active Surveillance Protocol

- (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. Pract Radiat Oncol [Internet]. 2018;1–7. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/30322661>

Figure 13 - Demonstration of OnCATs' AS tab for the prescription of radical AS.

4.5.3 Androgen deprivation therapy

For the prescription of ADT, firstly the user has to choose the desired type of ADT to be applied, which will then allow the determination of the first line approach, being it a drug or a procedure. If the user does not agree with any of the suggestions shown, a new type of ADT or approach can be manually added.

By combining the chosen type of ADT and first line approach with the patient's risk group and chosen treatment course, the system will be able to calculate the necessary treatment duration for non-surgical ADT approaches, if any of those are preferred. If a surgical approach is rather preferred, the treatment duration will always be stated as permanent.

After calculation, the option(s) for treatment duration will be displayed on the list, and the user must choose the most preferred one by selecting the corresponding radio button. If none of the displayed options satisfy the user, the treatment duration can be corrected manually.

After the ADT protocol is successfully prescribed and validated by the user, the user will be transported to the report page. A representation of the prescription of radical ADT using OnCATs can be consulted on figure 14.

4.5.4 Brachytherapy

For prescribing a BT treatment, the first step is to determine the dose-rate in which the treatment will be delivered, which should either be LDR or HDR. That choice will determine which radioactive isotopes are displayed to the user on the correspondent combo box. After that, the preferred radioactive isotope must be selected so that the system can calculate the optimal treatment dose(s).

By combining the information regarding the chosen type of BT and radioactive isotope with the patient's risk group and chosen treatment course, the system's algorithm will calculate the dose to be prescribed to the CTV, which for radical LDR BT is usually defined as the prostate gland with a 3 mm margin, and for HDR BT is usually defined as the prostate gland including or not the seminal vesicles.^{19,42}

After calculation, the available option(s) for treatment dose will be displayed on a list. The user must then choose an option by selecting the corresponding radio button. If the user finds that none of the available options are suitable for the patient, he can manually insert a different treatment dose and number of fractions.

An example of the output generated by OnCATs for the prescription of radical BT can be consulted on figure 15. When the radical BT treatment is successfully prescribed and validated, the user is taken to the report page.

ncats Prescription |
 [Home](#) |
 [Risk Assessment](#) |
 [Treatment Access](#) |
 Logged in as: admin

Patient Information
 ID: Treatment Course:
 Disease Site:
 Risk Classification:

Androgen Deprivation Therapy ✓

Type of ADT:

1st Line Approach:

ADT Duration: Choose one of the following or click [here](#) to insert a new one.

Do you confirm this information is correct?

References

Androgen Deprivation Therapy Protocol • (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54, 57–61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
 • Committee National Clinical Effectiveness. Diagnosis, staging and treatment of patients with prostate cancer National Clinical Effectiveness Committee [Internet]. 2015 [cited 2019 Dec 5]. Available from: <http://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/prostateguideline.pdf>
 • Alberta Health Services. Local Prostate Cancer [Internet]. 2018 [cited 2019 Dec 5]. p. 1–12. Available from: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu012-local-prostate.pdf>

Figure 14 - Demonstration of OnCATs' ADT tab for the prescription of radical ADT.

OnCATs Prescription | Home Risk Assessment Treatment Access | Logged in as: admin

Patient Information

ID: 75656 Treatment Course: BT

Disease Site: Prostate

Risk Classification: Intermediate Risk

Radical Brachytherapy

Dose Rate: High Dose Rate (HDR)

Radioactive Isotope: Iridium-192 Calculate

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

27 Gy, delivered in 2 fraction(s)

38 Gy, delivered in 2 fraction(s)

Do you confirm this information is correct? No Yes

References

Prescribed Radical Brachytherapy Dose:

- (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- American Brachytherapy Society and American College of Radiology. ACR-ABS Practice Parameter for Transperineal Permanent Brachytherapy of Prostate Cancer [Internet]. Vol. 1076, American Brachytherapy Society and American College of Radiology. 2015. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/281096322>

Figure 15 - Exemplification of the output generated by OnCATs for the prescription of radical BT.

4.5.5 External beam radiotherapy

For the prescription of an EBRT treatment, the first step is for the user to inform the system if prophylactic irradiation of the pelvic lymph nodes is to be performed or not, as this will greatly influence the generated output. While making that decision, if the user selects an option not recommended by the guidelines, for example, choosing to prophylactically irradiate the pelvic lymph nodes on a low risk patient, a pop-up alert emerges to advise the user that this course of action is not recommended by the literature.

If prophylactic lymph node irradiation is to be performed, the user has to define the treatment technique, which should be either 3DCRT, IMRT or VMAT, and also the treatment fractionation, which should be conventional, with dose per fraction of either 1,8 or 2 Gy.

Based on the chosen dose per fraction, the system calculates a range of possible doses to be prescribed to the lymph nodes. These are displayed on a list, and the user must choose an option, using the correspondent radio button. If for any instance the user does not agreed to any of the listed options, he can manually insert a new prescription dose.

After the dose prescribed to the lymph nodes is defined, or if it is decided that the lymph nodes are not to be irradiated at all, a new set of categories related to the prescription of the total treatment dose is displayed to the user. The next step is to calculate the total treatment dose. Similarly, to the previous step, the treatment technique and fractionation have also to be firstly chosen, using the available combo boxes. As the treatment can be done in phases, different techniques can be applied to either phases. Since the PTV for this phase is relatively smaller, generally being defined as the prostate gland, including or not the seminal vesicles, SBRT and hypofractionated approaches are now a viable option.^{10,17,37,38}

There are three different types of fractionation available: conventional, moderate hypofractionation and extreme hypofractionation. Although hyperfractionated EBRT regimens do exist, they are not indicated for prostate cancer patients, so if that option is selected, a pop up alert will emerges to advise the user to consider other kinds of fractionation.⁹ Regardless, if the user insists on using an hyperfractionated regimen, for example because it is beneficial for a specific patient, the total prescribed dose and dose per fraction have to be inserted manually. If a moderate or extreme hypofractionated regime is chosen, laterally on a text box are displayed recommendations of applicability for either of these approaches, so users can take that information into account while making a decision.^{10,37} After choosing the desired fractionation type, it is needed to choose the desired dose per fraction.

When the information regarding treatment technique, fractionation type and desired dose per fraction is available to the system, OnCATs' algorithm will calculate the optimal dose(s) for irradiation of the prostate gland.

The available option(s) will be displayed on a list and the user must choose the one that suits best the patient's needs, using the correspondent radio button. Once again, if the user finds that none of the options available are suitable, it is possible to manually insert the desired treatment dose and dose per fraction, as shown on appendix 15.

If the treatment is only to be delivered on a single phase, the total dose, dose per fraction, and total number of fractions are summarized on the bottom of the page, as shown on figure 16. If the treatment is delivered in phases, the dose prescribed to the lymph nodes is subtracted to the total dose, in order to determine the dose prescribed on the second phase of treatment, are summarized on the bottom the page, along with dose per fraction and number of fractions for each phase, as shown on figure 17. After the acceptance and validation of the prescription dose(s), the user is transported to the report page.

4.5.5.1 Combined courses of radiotherapy

However, EBRT is not always delivered as an isolate therapy, and can also be delivered in a combined treatment course with ADT, BT or both. Guidelines state that neoadjuvant, concurrent or adjuvant ADT can improve survival rates on courses of EBRT, so this addition is often considered for intermediate and high risk patients.⁹ When ADT is applied as an addition to EBRT, firstly the user has to prescribe the EBRT treatment and, after that, the ADT treatment is prescribed with the same workflow as described on chapter 4.4.3. A representation of the OnCATs' workflow for the prescription of EBRT with ADT can be consulted on appendix 16.

When BT is delivered after EBRT as a treatment boost, this often means that the pelvic lymph nodes will be irradiated with EBRT in a first phase, as this is not possible with BT, and then the prostate gland will be irradiated in a second treatment phase, using BT, with the aim of incrementing the dose delivered to the tumor. For this combined course of action, HDR BT is more commonly used than LDR BT.^{9,19} As for the OnCATs workflow for this approach, first the user has to prescribe the dose to the lymph nodes using EBRT and after that, the user will prescribe a second phase of treatment with BT, as described on chapter 4.4.4.

The dose delivered to the pelvic lymph nodes with EBRT should be between 40,5 – 50,4 Gy, using conventional fractionation. However, if the BT boost is being delivered with a single fraction of HDR BT, guidelines recommend that the EBRT dose should instead be 37,5 Gy, delivered in an hypofractionated scheme of 15 fractions of 2,5 Gy.⁹ A representation of the workflow for the prescription of EBRT with adjuvant BT can be consulted on appendix 17.

If ADT is also chosen to be part of the course, either as a neoadjuvant, concurrent or adjuvant therapy to either EBRT or BT, the ADT duration is assessed after the dose for both treatment phases is prescribed, as demonstrated on appendix 18.

OnCATs Prescription | Home | Risk Assessment | Treatment Access | Logged in as: admin

Patient Information

ID: 7675665336 Treatment Course: EBRT

Disease Site: Prostate

Risk Classification: Intermediate Risk

Pelvic Lymph Node Irradiation ✓

Lymph Node Irradiation: No

Target Volume External Beam Radiotherapy ✓

Treatment Technique: Volumetric Modulated Arc Therapy (VMA)

Fractionation: Conventional Fractionation

Dose Per Fraction: 2 Gy/Fraction **Calculate**

Total Dose: Choose one of the following or click [here](#) to insert a new one.

72 Gy 78 Gy
 74 Gy 80 Gy
 76 Gy

Total Prescribed Dose

74 Gy on 2 Gy per Fraction, in a total of 37 Fractions prescribed to the Target Volume.

References

Prophylactic Lymph Node Irradiation:
 • (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 64, 57–61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Total Prescribed Dose:

Figure 16 - Exemplification of OnCATs' tab for prescription of radical EBRT treatment. In this case is represented an intermediate risk prostate cancer patient who is being treated without prophylactic irradiation of the pelvic lymph nodes.

OnCATs Prescription | Home | Risk Assessment | Treatment Access | Logged in as: admin

Patient Information

ID: Treatment Course:

Disease Site:

Risk Classification:

Pelvic Lymph Node Irradiation ✓

Lymph Node Irradiation:

Treatment Technique:

Dose Per Fraction: Gy/Fraction

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

Gy Gy

Gy

Target Volume External Beam Radiotherapy ✓

Treatment Technique:

Fractionation:

Dose Per Fraction: Gy/Fraction

Total Dose: Choose one of the following or click [here](#) to insert a new one.

Gy Gy

Gy Gy

Gy

Total Prescribed Dose

Gy on Gy per Fraction, in a total of Fractions prescribed to the Regional Lymph Nodes.

+

Gy on Gy per Fraction, in a total of Fractions prescribed to the Target Volume.

=

Gy

Do you confirm this information is correct?

References

Prophylactic Lymph Node Irradiation:
 • (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54, 57–61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prescribed Dose to the Regional Lymph Nodes:

Figure 17 - Exemplification of OnCATs' tab for prescription of radical EBRT treatment. In this case is represented an intermediate risk prostate cancer patient who is being treated with prophylactic irradiation of the pelvic lymph nodes.

4.5.6 Radical prostatectomy

Since RP is a standard procedure with few variable parameters in terms of prescription, the available variables that need to be considered for assessment of the procedure are limited. Because of that, for the prescription of RP, the user has the possibility on the RP page of OnCATs to insert several notes regarding the surgical procedure. These notes may include any relevant information for the procedure, such as surgery technique, post-operative medication and any pre-operative preparation measures that may be necessary.

An example of the output generated by OnCATs for the prescription of RP can be consulted on figure 18. After the user inserts any relevant notes regarding the procedure, by clicking on the “Done” button, he is asked to review all the inserted information, and, after validation, is transported to the report page.

4.5.6.1 Combined radical prostatectomy courses

If PLND is to be performed in concurrence with RP, notes regarding the procedure, such as the limits of resection, should be included along with the notes regarding the RP procedure.

Adjuvant ADT can also be chosen to be part of the treatment course. When ADT is being delivered as an adjuvant therapy to RP, the prescription is performed after the user inserts the notes regarding the RP procedure, following the same workflow as the prescription of radical ADT described on chapter 4.4.3. An example of the output generated by OnCATs for the prescription of RP with concurrent PLND and adjuvant ADT can be consulted on appendix 19. EBRT is often chosen to be applied as an adjuvant therapy after RP, especially if positive margins are found after surgery.⁹ The goal of adjuvant EBRT after RP is usually to irradiate the lymph nodes and/or the prostate bed. The workflow for the prescription of adjuvant EBRT after RP is similar to the workflow described on chapter 4.4.5, but, in this case, the PTV will be prostate bed, instead of the prostate gland including or not the seminal vesicles.^{9,17} A representation of the workflow of the prescription of RP with adjuvant EBRT can be consulted on appendix 20.

Despite not being widely mentioned on the literature, hypofractionated regimens for post-operative RP can also be viable. If the user prefers this course of action, the option to insert a personalized dose regimen using a non-conventional fractionation regimen is available.

If ADT is also chosen to be part of the treatment course, neoadjuvant ADT is strongly discouraged, as it is instead preferred to be either delivered after or in concurrence with EBRT.^{9,13} An example of the workflow for prescription of RP with adjuvant EBRT and ADT can be consulted on appendix 21.

OnCATs Prescription | Home Risk Assessment Treatment Access Report1 | Logged in as: admin

Patient Information

ID: 33443233 Treatment Course: RP

Disease Site: Prostate

Risk Classification: Low Risk

Radical Prostatectomy Description ✓

The procedure will include the removal of the whole prostate gland using a retropubic approach. The patient will be positioned on the surgical table on prone position, and the procedure will be performed using general anesthesia

References

Radical Prostatectomy Description:

- Radical Prostatectomy description defined by criteria defined by the user admin on 24/02/2020.

Figure 18 - Exemplification of OnCATs' tab for prescription of primary RP. In this case is represented a low risk prostate cancer patient.

Observation is also a viable option for adjuvant therapy after RP. For this treatment course, the first step is to insert the notes regarding the RP procedure, just as previously described. If concurrent PLND chosen to be performed in concurrence with RP, the notes regarding the procedure should also be included along with the notes for the RP procedure. After that, the next step is to approve or refuse the suggested Observation protocol, just as described on chapter 4.4.1. An example of this workflow can be consulted on appendix 22.

4.6 Generating a report

The report is the last phase on the OnCATs workflow. On the final report is carefully described all information obtained until now through all the phases of OnCATs. Throughout all the system's workflow, every time the user confirms that an output is correct, by clicking on the available "Yes" buttons, the information is automatically imported to the report page, and is stored in the correspondent text box. When confronted with the "Report" tab, the user is asked to review all the listed information, in order to analyze once more if the generated output matches the expectations.

Firstly, on the displayed report, are shown the demographic characteristics regarding the patient, with the picture located laterally, which are the key to identify the patient report. Right below it, are described the characteristics of the patient's disease that led to choosing the treatment course. Included in this section, are also the referred risk group and the chosen treatment course. On the middle of the page of the report, are displayed all the parameters for the prescription of each individual treatment modality that is part of the chosen treatment course, included the generated outputs by OnCATs and the choice made by the user in each task of the system's workflow.

The user has also the option to insert on an available notes text box any notes regarding information that may seem relevant for the treatment of the patient, but that somehow were not previously assessed during the process. The user can also consult for a last time the references in which the shown information is based. Lastly, the user is asked once more to review all the information and confirm if everything is in order. If the user affirms that any of displayed information is not correct, by clicking on the "No" button, all the text boxes containing non-demographic information turn blank so that is possible manually insert correct information. Otherwise, if all the information is correct, by clicking on the "Yes" button, the button "Print" becomes visible, which allows the exportation the report in ".pdf" format.

At the end of this process, the user should be in possession of a fully detailed report regarding an action course for a specific prostate cancer patient. An example of the report is displayed on figure 19.

OnCATs Treatment Prescription Report


Username:

Patient Information

ID: Name(s): Surname(s): Date of Birth:

Gender: Nationality: Ethnicity: Age: years

Patient Picture



Disease Info

Disease Site: Clinical Stage: T N M Total Gleason Score: ISUP Conesus Grade:

PSA Value: ng/ml Patient Life Expectancy: years Symptomatology: Adverse Features:

Risk Classification: Treatment Course: + +

Radical Prostatectomy

The procedure will include the removal of the whole prostate gland using a retropubic approach. The patient will be positioned on the surgical table on prone position, and the procedure will be performed using general anesthesia.

Target Volume External Beam Radiotherapy

Treatment Technique:

Dose per Fraction: Gy

Prescribed Dose: Gy

Number of Fractions:

Notes

The patient presented himself with urinary symptoms. The disease had positive margins and PSA went from 0,5 ng/ml to 3,5 ng/ml after surgery. Patient has high risk of heart failure and suffers from interstitial pulmonary disease.

Lymph Node External Beam Radiotherapy

Treatment Technique:

Dose per Fraction: Gy

Prescribed Dose: Gy

Number of Fractions:

Total Radiotherapy Prescription

Total Prescribed Dose: Gy

Total Number of Fractions:

Androgen Deprivation Therapy

Type of ADT:

1st Line Approach: +

Treatment Duration:

Local, Date (DD/MM/AAAA): _____, ____/____/____

Signature: _____

Figure 19 - Example of a final report generated by OnCATs for a patient who underwent RP with adjuvant EBRT and ADT.

4.7 Testing the system

A total of 10 clinical cases, based on reports published between 2008 and 2019, were obtained to be tested with OnCATs. A summary of the demographics and disease related characteristics of the clinical cases used for testing the OnCATs system can be consulted on table 5.^{32,83–91}

Table 5 - Summary of the characteristics of the clinical cases obtained for testing the OnCATs' algorithm.

Study Identification			Demographic Data			Disease Related Data	
ID	Author	Year of Publication	Age (Years)	Nationality	Ethnicity	Symptomatology	Adverse Features
CC01	Tisman et al.	2009	75	Chinese	Asian	Asymptomatic	Present
CC02	Nishimura et al.	2014	68	Japanese	Asian		
CC03	Hiyama et al.	2011	59	Japanese	Asian	Symptomatic	Present
CC04	Chang et al.	2016	70		Caucasian		Present
CC05	Coyle et al.	2015	64		Afro-Caribbean		
CC06	Tisman et al.	2011	71		Caucasian		Present
CC07	Brahmbhatt et al.	2008	71		African	Symptomatic	Present
CC08	Shen et al.	2019	77				Present
CC09	Castro-Alonso et al.	2019	65				
CC10	Yamashita et al.	2017	77				

The sample of patients has a mean age of $69,7 \pm 5,9$ years (59 – 77 years), 70 % of the reports did not mention the nationality of the patient and 30 % did not mention the ethnicity.^(86–94)

As for the presence of symptoms, 7 out of 10 (70 %) reports did not mention if the patient manifested symptoms at the time of assessment. For CC02, CC04, CC05, CC08 and CC09, we assumed those patients were symptomatic, since they displayed high and very high-risk characteristics and higher tumor stages. For CC06 and CC10, we assumed those patients were asymptomatic, since they manifested characteristics of intermediate risk patients and lower tumor stages.^{84,86,87,89,90}

As for the presence of adverse features, 4 out of 10 (40 %) of the case reports did not mention if adverse features were present or not. For CC02, CC05, CC09 and CC10, we assumed those patients did not exhibit any adverse features since they were not mentioned on the case report.^{84,87,90,91}

Regarding the life expectancy, the results of the estimation of the patient life expectancy using the method of Kim *et al.* can be consulted on table 6.^{32,83-91}

Table 6 - Results of the calculation of the life expectancy of the clinical cases used for testing OnCATs, using the method of Kim *et al.*

	CC01	CC02	CC03	CC04	CC05	CC06	CC07	CC08	CC09	CC10
Age (Years)	75	68	59	70	64	71	71	77	65	77
GS	5	7	7	9	9	7	8	9	8	6
Lead Time (Years)	10	0	0	0	0	0	0	10	0	10
Quartile of Health	Healthy	Not Healthy	Not Healthy	Not Healthy	Very Healthy	Very Healthy	Not Healthy	Healthy	Not Healthy	Healthy
Risk of Mortality by Cancer (%)	1,2	6,5	6,5	12,1	12,1	6,5	12,1	12,1	12,1	3
Life Expectancy (Years)	10,1	4,4	5,2	2,8	9,4	11,7	2,8	8,5	3,1	8,9
Life Expectancy Category (Years)	> 9	< 6	< 6	< 6	> 9	> 9	< 6	6 - 9	< 6	6 - 9

The mean estimated life expectancy for this sample of patients was $6,7 \pm 3,4$ years (2,8 – 11,7 years). Following those results, 5 out of 10 patients (50%) were placed on the category of life expectancy bellow 6 years, 2 patients (20%) were placed on the category of life expectancy between 6 and 9 years and 3 patients (30%) were placed on the category of life expectancy above 9 years.^{32,83-91}

Regarding the quartile of health, 5 patients (50 %) were considered to be on the bottom quartile of health (not healthy) due from suffering from comorbidities, such as myocardial infarction, *diabetes mellitus* type 2, urinary complications such as dysuria and nocturia, hypertension, hepatic cirrhosis, obesity and dyslipidemia. 3 patients (30 %) were considered to be in the middle quartile of health (healthy) due to being mentioned if they suffered from any comorbidities, and the 2 other patients (20 %) were considered to be in top quartile of health (very healthy) due to being described as not suffering from any comorbidities.^{32,83-91}

As for the risk of mortality by prostate cancer, 1 patient (10 %) was found to have a 1,2 % chance of dying by prostate cancer in the expected years of life, 1 patient (10 %) was found to have a 3 % chance of dying by prostate cancer in the expected years of life, 3 patients (30 %) patients were found to have a 6,5 % chance of dying by prostate cancer in the expected years of life and 5 patients (50%) were found to have a 12 % chance of dying by prostate cancer in the expected years of life.^{32,83-91}

4.7.1 Risk group assessment

Regarding the risk group assessment, OnCATs was able to successfully characterize each patient into a risk group using the NCCN nomenclature. The results of the risk group stratification for each clinical case is demonstrated on table 7.^{9,32,91,83-90}

Table 7 - Results of the risk group assessment for the clinical cases used for testing OnCATs, using the NCCN nomenclature.

ID	Tumor Stage	GS	PSA Value (ng/ml)	PSA Category (ng/ml)	Risk Group
CC01	T1c N0 M0	5	4	< 10	Very Low
CC02	T2b N0 M0	7	62,1	> 20	High
CC03	T2b N0 M0	7	9,5	< 10	Intermediate
CC04	T2b N0 M0	9	1,8	< 10	High
CC05	T4 N0 M0	9	< 10	< 10	Very High
CC06	T1c N0 M0	7	8	< 10	Intermediate
CC07	T4 N0 M0	8	5874	> 20	Very High
CC08	T4 N0 M0	9	52,736	> 20	Very High
CC09	T4 N0 M0	8	32	> 20	Very High
CC10	T1c N0 M0	6	10,35	10 - 20	Intermediate

This sample has a mean GS of $7,5 \pm 1,4$ and a mean PSA value at the time of assessment of is $606,5 \pm 1850,9$, including outliers (CC07), and $21,2 \pm 22,4$, excluding outliers. 4 out of 10 patients (40 %) have a tumor stage of T4 N0 M0, 3 patients (30 %) have a tumor stage of T2b N0 M0 and the other 3 patients (30 %) have a tumor stage of T1c N0 M0.^(9,94,86-93)

According to the system's algorithm, 1 patient (10%) was characterized as having a very low risk disease, 3 patients (30%) were characterized as having intermediate risk diseases, 2 patients (20%) were characterized as having high risk diseases and 4 patients (40%) were characterized as having very high risk diseases.^(9,94,86-93)

4.7.2 Treatment course assessment

Regarding the OnCATs performance on assessing the available treatment courses for all clinical cases, the detailed results can be consulted on table 8.^{9,76,91,83-90}

As for the applied treatment course, 3 out of 10 patients (30 %) were submitted to radical ADT, 2 patients (20 %) were submitted to EBRT with neoadjuvant ADT, 1 patient (10 %) was submitted to radical Observation, 1 patient (10 %) was submitted with RP with PLND and adjuvant EBRT with ADT, 1 patient (10 %) was submitted to EBRT with adjuvant ADT and 1 patient (10 %) was submitted to EBRT with adjuvant BT.^{9,76,91,83-90}

Table 8 - Results of the treatment course assessment for the clinical cases used for testing the OnCATs algorithm.

ID	Risk Group	Life Expectancy Category (Years)	Symptomatology	Presence of Adverse Features	Applied Treatment Course	Treatment Courses Suggested by OnCATs	Pass/Fail
CC01	Very Low	> 9	Asymptomatic	Present	Observation	AS	Fail
						EBRT	
						RP + Observation	
						RP + EBRT	
						RP + EBRT + ADT	
CC02	High	< 6	Symptomatic	Not Present	ADT + EBRT	EBRT + ADT	Pass
						EBRT + BT + ADT	
						RP + PLND	
CC03	Intermediate	< 6	Symptomatic	Present	RP + EBRT + ADT	Observation	Fail
						BT	
						EBRT + ADT	
						EBRT + BT + ADT	
CC04	High	< 6	Symptomatic	Present	ADT + EBRT	EBRT + ADT	Pass
						EBRT + BT + ADT	
						RP + PLND + ADT	
						RP + PLND + EBRT + ADT	
						RP + PLND + Observation	
CC05	Very High	> 9	Symptomatic	Not Present	ADT	EBRT + ADT	Fail
						EBRT + BT + ADT	
						RP + PLND	
CC06	Intermediate	> 9	Asymptomatic	Present	ADT	AS	Fail
						BT	
						EBRT + ADT	
						EBRT + BT	
						EBRT + BT + ADT	
						RP + Observation	
						RP + PLND + Observation	
						RP + PLND + EBRT + ADT	
CC07	Very High	< 6	Symptomatic	Present	ADT	EBRT + ADT	Fail
						EBRT + BT + ADT	
						RP + PLND + ADT	
						RP + PLND + EBRT + ADT	
						RP + PLND + Observation	
CC08	Very High	6 - 9	Symptomatic	Present	RP + PLND + EBRT + ADT	EBRT + ADT	Pass
						EBRT + BT + ADT	
						RP + PLND + ADT	
						RP + PLND + EBRT + ADT	
						RP + PLND + Observation	

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ID	Risk Group	Life Expectancy Category (Years)	Symptomatology	Presence of Adverse Features	Applied Treatment Course	Treatment Courses Suggested by OnCATs	Pass/Fail
CC09	Very High	< 6	Symptomatic	Not Present	EBRT + ADT	EBRT + ADT	Pass
						EBRT + BT + ADT	
						RP + PLND	
CC10	Intermediate	6 - 9	Asymptomatic	Not Present	EBRT + BT	Observation	Fail
						EBRT	
						BT	

By analyzing each applied treatment course as individual modalities, it is possible to observe that that 8 out of 10 patients (80 %) were submitted to ADT, 6 patients (60 %) were submitted to EBRT, 2 patients (20 %) were submitted to RP, 1 patient (10 %) was submitted to Observation, 1 patient (10 %) was submitted to PLND and 1 patient (10 %) was submitted to BT.^{9,76,91,83-90}

After analyzing the treatment course assessment using the OnCATs algorithm, it was observed that the system was able to successfully suggest the applied treatment course (pass) in 4 out of 10 clinical cases (40 %), and was not able to suggest the applied treatment course (fail) in 6 out of 10 clinical cases (60 %).

The mean number of options that OnCATs suggested for all cases was $4,4 \pm 1,6$. For the cases in which OnCATs suggested the treatment course that was applied to the patient, the mean number of options suggested was $4 \pm 1,2$. For the cases where OnCATs did not suggest the treatment course that was applied to the patient, the mean number of options suggested was $4,7 \pm 1,9$.

4.7.3 Treatment prescription

The analysis of the system's performance on prescribing each treatment was split into four groups, based on the individual treatment modalities that were part of each treatment course. For CC01, since the case report did not mention the Observation protocol that was as applied for the treatment of the patient, the comparison with the default protocol suggested by OnCATs was not possible, so further results regarding the treatment prescription for this clinical case were not possible to obtain.⁸³

The results of the test of performance for OnCATs prescription of EBRT can be consulted on table 9.^{84-86,89,91} As for ADT, the results for the test of performance for OnCATs can be consulted on table 10.^{85-90,92}

Table 9 - Results of the performance of OnCATs algorithm for the prescription of EBRT.

EBRT Prescription															
ID		Treatment Technique				Fractionation			Dose per Fraction (Gy)		Prescribed Dose (Gy)				
CC02	Report	IMRT				Conventional Fractionation			2		74				
	OnCATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation	Moderate Hypofractionation	Extreme Hypofractionation	1,8	2	72	74	76	78	80
	Pass/Fail	Pass				Pass			Pass		Pass				
CC03	Report	Not mentioned				Conventional Fractionation			2		50				
	OnCATs Suggestions	3DCRT	IMRT	VMAT		Conventional Fractionation			1,8	2	64	66	68	70	72
	Pass/Fail	Not assessible				Pass			Pass		Fail				
CC04	Report	3DCRT				Conventional Fractionation			2		76				
	OnCATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation	Moderate Hypofractionation	Extreme Hypofractionation	1,8	2	72	74	76	78	80
	Pass/Fail	Pass				Pass			Pass		Pass				
CC08	Report	Not mentioned				Conventional Fractionation			2		74				
	OnCATs Suggestions	3DCRT	IMRT	VMAT		Conventional Fractionation			1,8	2	64	66	68	70	72
	Pass/Fail	Not assessible				Pass			Pass		Fail				
CC10	Report	Not mentioned				Conventional Fractionation			2		50				
	OnCATs Suggestions	3DCRT	IMRT	VMAT	SBRT	Conventional Fractionation			1,8	2	46	48	50		
	Pass/Fail	Not accessible				Pass			Pass		Pass				

Table 10 - Results of the performance of OnCATs algorithm for the prescription of ADT.

ID		Type of ADT				1st Line Approach										Treatment Duration			
CC02	Report	Not mentioned				Not mentioned										Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Bilateral Orchiectomy	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	Degarelix	1,5 Years	2 Years	2,5 Years	3 Years	
	Pass/Fail	Not accessible				Not accessible										Not accessible			
CC03	Report	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide			Flutamide			Bicalutamide				3,5 Years			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	OnCATs was not able make a suggestion						
	Pass/Fail	Pass				Pass										Fail			
CC04	Report	LHRH Agonist				Leuprolide										9 Months			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide			Triptorelin				1,5 Years	2 Years	2,5 Years	3 Years	
	Pass/Fail	Pass				Pass										Fail			
CC05	Report	LHRH Agonist				Goserelin										Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide			Triptorelin				1,5 Years	2 Years	2,5 Years	3 Years	
	Pass/Fail	Pass				Pass										Not accessible			

(Continues on next page)

ID		Type of ADT				1st Line Approach								Treatment Duration			
CC06	Report	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide				Flutamide				Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	6 Months				
	Pass/Fail	Pass				Pass								Not accessible			
CC07	Report	LHRH Agonist + Non-Steroidal Antiandrogen				Leuprolide				Bicalutamide				Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	1,5 Years	2 Years	2,5 Years	3 Years	
	Pass/Fail	Pass				Pass								Not accessible			
CC08	Report	LHRH Agonist + Non-Steroidal Antiandrogen				Goserelin			Leuprolide		Bicalutamide			Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Goserelin	Histrelin	Leuprolide	Triptorelin	Nilutamide	Flutamide	Bicalutamide	6 Months				
	Pass/Fail	Pass				Pass								Not accessible			
CC09	Report	LHRH Antagonist				Degarelix								Not mentioned			
	OnCATs	Surgery	LHRH Agonist	LHRH Agonist + Non-Steroidal Antiandrogen	LHRH Antagonist	Degarelix								1,5 Years	2 Years	2,5 Years	3 Years
	Pass/Fail	Pass				Pass								Not accessible			

4.7.3.1 Prescription of external beam radiotherapy

Regarding EBRT prescription, in general, OnCATs was able to successfully perform (pass) 15 out of the 20 tasks (75 %) that consisted the workflow of CC02, CC03, CC04, CC08 and CC10 on OnCATs. In 2 of the tasks (10%), the system did not suggest the option that was applied to the patient's treatment (fail) and in 3 tasks (15 %) a comparison was not possible due to that information not being disclosed on the case report. More specifically, regarding the treatment technique, fractionation and dose per fraction, OnCATs was able to suggest the applied choice in all the clinical cases simulations. Regarding the dose prescription, OnCATs had a 60% pass rate, meaning that 3 out of 10 cases had a successful dose prescription and 2 cases (40 %) had a failed dose prescription.

By analyzing each case individually, on 60 % of the cases (CC02, CC04 and CC10), OnCATs was able to recreate all the phases of the clinical workflow that those patients were submitted to. On the other 40 % (CC03 and C008), OnCATs did not only suggest the applied prescription dose, but succeeded on the other phases of the workflow.^{84-86,89,91}

4.7.3.2 Prescription of androgen deprivation therapy

As for the prescription of ADT, OnCATs managed to successfully perform (pass) 14 out of the 21 tasks (66,67 %) that consisted the workflow of CC03, CC04, CC05, CC06, CC07, CC08 and CC09. In 2 of the tasks (9,52 %), the system did not suggest the option that was applied to the patient's treatment (fail) and in 5 tasks (23,91 %) a comparison was not possible due to that specific information not being disclosed on the case report. More specifically, regarding the type of ADT and first line approach, OnCATs was able to successfully suggest the option applied to the clinical case in all the clinical cases. However, on the prescription of the treatment duration, in the 2 cases where we had indication of the total treatment duration (CC03 and CC04), OnCATs was not able to recommend the right treatment duration in either of them.

By making an analysis by case, it is possible to note that OnCATs was not able to recreate all phases on the clinical workflow in either of the clinical cases. This was caused either by the treatment duration being not mentioned on the case reports, or the system recommending a different treatment duration than the one that was applied.^{85-90,92}

4.7.3.2 Prescription of brachytherapy

On our sample of clinical cases, only a single case (CC10) underwent a BT treatment. Lastly, the results of the OnCATs analysis for the BT treatment of CC10 can be consulted on table 11.⁹¹

Table 11 - Results of the performance of OnCATs algorithm for the prescription of BT.

BT Prescription							
CC10		Type of BT		Radioactive Isotope	Prescribed Dose and Number of Fractions		
	Case Report	HDR		Iridium-192	18 Gy in 2 Fractions		
	OnCATs	LDR	HDR	Iridium-192	12 Gy in 1 Fraction	15 Gy in 1 Fraction	21,5 Gy in 2 Fractions
	Pass/Fail	Pass		Pass	Fail		

For the adjuvant BT prescription of CC10, it is possible to observe that OnCATs was able to suggest the right type of BT and radioactive isotope (pass), but not the right dose prescription and number of fractions (fail).⁹¹

4.7.4 General analysis

On table 12 is demonstrated a summary of the rate of success (pass) and failure (fail) on the all tasks performed during the testing of the OnCATs' algorithm.⁽⁸⁶⁻⁹⁴⁾

Table 12 - Summary of the performance of OnCATs on performing the tasks that constituted the testing of the system.

		Pass	Fail	Total	Passing Rate (%)
Risk Group Assessment		10	0	10	100
Treatment Course Assessment		4	6	10	40
EBRT Prescription	Treatment Technique	2	0	2	100
	Fractionation	5	0	5	100
	Dose per Fraction	5	0	5	100
	Dose Prescription	3	2	5	60
ADT Prescription	Type of ADT	7	0	7	100
	1st Line Approach	7	0	7	100
	Treatment Duration	0	2	2	0
BT Prescription	Type of BT	1	0	1	100
	Radioactive Isotope	1	0	1	100
	Dose Prescription	0	1	1	0
Total		45	11	56	76,3

It is possible to observe that, in general, OnCATs successfully performed 45 out of 56 tasks (80,4 %) and failed in 11 tasks (19,6 %). The tasks where OnCATs performed better were on risk group assessment (100 %), definition of EBRT technique (100 %), EBRT fractionation (100 %), EBRT dose per fraction (100 %), definition of type of ADT (100 %), first line approach (100 %), definition of type of BT (100 %) and definition of the radioactive isotope for BT treatments (100 %), followed by the dose prescription for EBRT (60 %) and treatment course assessment (40 %). The tasks where OnCATs performed poorly were the assessment of ADT treatment duration (0 %) and the assessment of dose prescription in BT treatments (0 %).

On the other hand, it is also important to analyze each individual clinical case. On table 13 are summarized the number of successful and failed tasks, by clinical case, performed by OnCATs during the testing of the algorithm.^(86–94)

Table 13 - Number of successful and failed tasks by the OnCATs system, by clinical case.

	Number of Successful Tasks	Number of Failed Tasks	Total	Passing Rate (%)
CC01	1	1	2	50
CC02	6	0	6	100
CC03	5	3	8	62,5
CC04	8	1	9	88,9
CC05	3	1	4	75
CC06	3	1	4	75
CC07	3	1	4	75
CC08	6	1	7	85,7
CC09	4	0	4	100
CC10	6	2	8	75
Total	45	11	56	80,4

By analyzing the shown results, it is possible to observe that each clinical case had a mean passing rate of 78,7 % ± 15,6 %. The clinical cases where the OnCATs algorithm performed better were CC02 and CC09 (100 %), followed by CC04 (88,9 %), CC08 (85,7 %), CC05, CC06, CC07 and CC10 (75 %), CC03 (62,5 %) and CC01 (50 %).

5. Discussion

To the extent of our knowledge, OnCATs is the only developed system that is applied to assisting decision making in all phases of prostate cancer treatment, including risk group assessment, treatment course assessment and treatment prescription.

On the study of Wijk *et al.*, seven clinical DSSs, used for assisting in decision making in several different parameters of the treatment of prostate cancer, were reviewed in 2019.⁸ The reviewed studies displayed a wide range of applications within the prostate cancer treatment workflow. Among others, the authors reviewed published studies that included models to compare different EBRT plans, using parameters such as Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP), which allowed choosing the treatment plan with the best predicted outcome. Models to optimize IMRT plans based on the outcomes of disease progression, free survival and toxicity were also reviewed, displaying promising results. A model to predict the dosimetric advantage of the placement of a perirectal spacer before the implementation itself was also reviewed, which showed to be a valuable tool for the implementation of advanced EBRT techniques such as SBRT. In this study, is also mentioned a model to predict the advantages of applying adjuvant EBRT after the main treatment course, based on a nucleic acid detection immunoassay, and models to evaluate cost-effectiveness of IMRT treatments in different conditions.⁸

Overall, the authors found that the majority of the published studies related to the assisting decision making in prostate cancer treatment at the time, were limited to specific phases of the EBRT treatments, such as treatment plan selection, prediction of the outcomes of both photon beam and proton beam treatments, comparison between SBRT and IMRT treatments and the use of perirectal spacers. Following those results, they emphasize on the need of development of new methods and tools that include other treatment modalities, such as RP, BT and ADT and comparisons between the outcomes and results that may be achieved by choosing different treatment courses and prescriptions.⁸

In 2014, Kent *et al.* published a study where 14 publications related to models for estimating a prostate cancer patient life expectancy were reviewed.⁹³ Of the 14 studies, only 3 studies used life tables to predict the life expectancy. The authors found that most approaches did not take into account if the patient had any relevant comorbidities that could compete with the cancer for mortality cause. The simple act of defining to which quartile of health a given patient belongs to, leads to a biased result, since it is only based on a simple subjective analysis. On this study, the method of Kim *et al.* for calculating the estimate life expectancy for prostate cancer patients was also reviewed. Regarding this method, the authors found its results to be implausible,

since they found no reliable connection between the output risk of death by prostate cancer and the patient's age, which is not in concordance with clinical experience. In general, the authors found that even though clinical guidelines include the estimated life expectancy of a patient as a key factor for assessment of the optimal treatment course, no appropriate tool exists to accurately estimate this value, and this may constitute a setback for the development of Clinical DSS tools.⁹³

Regarding the performance of OnCATs, it was noted that the majority of the analyzed clinical reports used for testing the system's algorithm omitted relevant information that would allow a more detailed analysis of the system. Regarding the few cases where OnCATs output did not match the same option that was part of the patient's course of action, it was analyzed in detail every case report in order to investigate which reasons might have led to that occurrence.

For CC01, since Observation is reserved for older patients with one or more comorbidities that will compete with the cancer for mortality cause, the system did not suggest that option, given the estimated life expectancy for patient was 10,1 years.^{9,11,13,32,40} Despite having no indication that this patient was not healthy, if we assumed that this patient belonged to the bottom quartile of health (not healthy), the estimated life expectancy would be 4,7 years.³² As for the presence of symptoms at the time of diagnosis, on the case report it was only stated that the patient had no urological complaints, which usually are the first symptoms to be manifested on a prostate cancer patient. If we assumed that this patient had an estimated life expectancy inferior to 6 years and was symptomatic, OnCATs would be able to suggest Observation as a viable treatment approach. Based on these facts, the mismatch of results could be due to the fact of the estimation of the patient's life expectancy and symptomology not being accurate, given the missing information from the case report.

Regarding CC03, OnCATs was not able to suggest RP with adjuvant EBRT and ADT as a viable chosen treatment course. This is due to RP being more indicated to patients with an estimated life expectancy superior to 9 years, and adjuvant EBRT with ADT being reserved to patients who display adverse features.^{9,11,75} On the case report is mentioned that the patient has high risk of heart failure and interstitial pulmonary disease, because of that, it was fair to assume that the patient was on the bottom quartile of health (not healthy).⁸⁵ If it was instead assumed that the patient was on the middle quartile of health (overall healthy), the estimated life expectancy would be 16,4 years.³² By assuming the patient had an estimated life expectancy superior to 9 years, was symptomatic and had adverse features, RP with adjuvant EBRT and ADT would have been suggested by OnCATs. Once again, the mismatch of results could be related with the estimation of the patient's life expectancy.

As for the EBRT prescription, 50 Gy is not commonly prescribed for the irradiation of the prostate bed, but is common on initial treatment phases in which the pelvic lymph nodes are irradiated.¹³ On this case, it was possible to assume, since a PLND was not performed, that EBRT was applied as an adjuvant therapy, to irradiate the whole pelvis, which includes both the pelvic lymph nodes and the prostate bed, without applying a boost to the prostate bed.

For CC04, regarding the ADT prescription, OnCATs was not able to suggest a treatment duration of 9 months. Based on the guidelines, for high risk patients, the ADT treatment should be prescribed for at least 1,5 years and up to 3 years.^{9,13,16} On the case report, is stated that the patient was submitted to ADT with leuprolide for 9 months, another ADT drug or approach could have been prescribed after that, without being reported on the case report.⁸⁶

As for CC05, CC06 and CC07, the system could not recommend radical ADT as a viable treatment option, since, by the guidelines, radical ADT is only indicated for high and very high patients with life expectancy inferior to 6 years and asymptomatic.^{9,49,88}

On the reports of CC06 and CC07, there was no indication if the patients had any comorbidities or symptoms. If we were to assume that both patients belonged on the last quartile of health (not healthy), despite having no indication to support that statement, the estimated life expectancy would instead be 3,1 and 3,9 years respectively.³² Following that, by assuming both patients had an estimated life expectancy inferior to 6 years, and both diseases were asymptomatic, which would be unusual giving the tumor stage, OnCATs would have been able to correctly suggest radical ADT as a treatment approach.

For CC08, OnCATs did not suggest the prescribed dose for adjuvant EBRT. Based on the NCCN[®] Guidelines for Prostate Cancer, the prescribed dose for adjuvant EBRT after RP should be between 64 and 72 Gy, delivered in conventional fractionation.⁹ For this clinical case, the prescribed dose was 74 Gy, which means that comparing to the guidelines, an additional fraction of 2 Gy was delivered.⁸⁹ The reasons behind the dose prescription were not discussed on the case report, so it is not possible to assess if this had any relevant clinical advantage.

Lastly, regarding CC10, OnCATs was not able to suggest EBRT with adjuvant BT as a viable treatment option, since this therapy is reserved for intermediate risk patients with life expectancy superior to 9 years and with adverse features.^{9,14,16,75} Since there was no mention if the patient had any comorbidities or adverse features, it was assumed that the patient was in the middle quartile of health (overall healthy) and had no adverse features. If instead it was assumed that the patient was on the top quartile of health (very healthy), the estimated life expectancy would have been 11,4 years.³² Assuming the patient had an estimated life expectancy superior to 9 years and had adverse features, OnCATs would be able to suggest EBRT with adjuvant BT as a valid option for treatment course.⁹

6. Conclusions

In general, it was observed that OnCATs can accurately simulate the clinical workflow for risk group assessment, treatment assessment and prescription, for localized prostate cancers patients, providing clear evidence-based information, useful for any kind of task in the oncology workflow of treatment. The system also constitutes a method for a healthcare professional to assess all treatment variable options in a short period of time before making a definitive decision, which allows saving time and resources, optimizing the overall flow of work. The assistance options and information given to the user, along the system's workflow, are useful and relevant for decision making assistance and have the possibility to make a positive impact on both available knowledge at the time of assessment and time spent on this specific task. Besides that, OnCATs also gives its output on a universal well-known medical language, easy to comprehend by all healthcare professionals on the medical oncology field, which allows the generated outputs to be shared between professionals in an efficient way and to be easily used on future clinical research.

VB constitutes a fairly easy-to-use programming language that facilitates the development of CDDs. The development of the algorithm with this technology, proved to be an efficient way to computerize a medical process, and make it assessible to healthcare professionals, by the means of an easy-to-use digital tool. This study allowed the comprehension of the workflow to which a cancer patient is put through when diagnosed with a tumor. Besides prostate cancer being chosen as the starting point, on the development of applications for the system, due to providing a solid learning curve, all the steps necessary to expand this method to other kinds of diseases are now well established, showing great promise on its future applications.

Regarding the tests performed on the system, for the risk assessment it was found that OnCATs can accurately assign a risk group to a specific prostate cancer patient using the NCCN nomenclature, and this serves as the correct starting point for choosing the optimal treatment course for a patient.⁹ As for treatment course assessment, we found that the estimation of the patient's life expectancy can highly impact the output generated by the system. The method developed by Kim et al. showed to not always provide a reliable result to this system's workflow, as it forces the estimation of subjective parameters such as the definition of the quartile of health in which the patient belongs.³² Since any optimal methods for estimating to automatically estimate the life expectancy of a prostate cancer patient were not found, new methods should be investigated and researched in the future.

Despite the positive results, the testing of OnCATs system could also be optimized if more clinical reports containing key information for the system's testing were available. Most of the reviewed clinical case reports did not mention crucial information that would allow the

comparison of the workflow in all stages of prostate cancer treatments, such as the presence of symptoms during the time of diagnosis and the duration of the applied treatment protocol. Also, case reports where the patients were treated with EBRT courses that were not delivered with conventional fractionation were not found, so the possibility to use OnCATs as a mean to evaluate the applicability of hypofractionated regimens in a preterminal clinical workflow was not tested. As for the prescription of treatments, it was noticed that OnCATs was found to perform slightly better on the prescription of EBRT treatments, in comparison to ADT treatments. This can be due to the fact that EBRT treatments are usually better reported on clinical case reports in comparison to EBRT treatments.

Regardless of the results obtained by applying clinical cases to the systems, it is important to mention that majority of prostate cancer patients has multiple treatment options and different prescriptions. This translates to different physicians being able to choose different courses of action for the same patient, while applying different prescriptions, based on their experience and judgement, without compromising the patient's outcomes and quality of life.

It is important to refer that more studies are needed on the development of clinical DSSs for the assessment and prescription of prostate cancer treatments, in order to evaluate which parameters are not being considered for the workflow management and which pathways could be improved, in order to develop a more automated and accurate system.

In the future, the goal is to develop new measures for the system to automatically update its knowledge base. At the moment, since individual practices are not always exploitable to bigger populations, the knowledge has to be manually updated when a new clinical guideline is published, by manually changing the system's algorithm and code source. Ideally, the system would have a practical way of automatically scanning published documents and storing information automatically on the knowledge base, by using means of artificial intelligence and machine learning. Functionalities regarding the analysis of similar patterns between users and distinctions that lead to similarities in the processes of decision-making could also be include on the system's algorithm. New implementations such as the one suggested, could lead to identifying new variables that are relevant to the system's workflow, and that could optimize its functionality. The use of big data has become the standard in healthcare technology as it helps to predict outcomes and results in bigger populations of patients. In the future, the system would benefit from testing using a bigger sample of patients, of different risk groups, and treated with different treatment courses and approaches. We would also like to extend the system's use to non-localized and non-adenocarcinoma prostate cancers, and other types of cancer, such as breast cancer or rectal cancer, since all types of cancer could benefit from an automated and assisted method for treatment assessment and prescription.

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8. Appendixes

8.1 Appendix 1

Table 14 – Characteristics of the TNM clinical staging system for prostate cancer.

TNM	Clinical Stage	
T ⁻ Prima	TX	Primary tumor cannot be assessed

	T0	No evidence of primary tumor
	T1	Clinically inapparent tumor that is not palpable
	T1a	Tumor incidental histologic finding in 5% or less of tissue resected
	T1b	Tumor incidental histologic finding in more than 5% of tissue resected
	T1c	Tumor identified by needle biopsy found in one or both sides, but is not palpable
	T2	Tumor is palpable and confined within prostate
	T2a	Tumor involves one-half of one side or less
	T2b	Tumor involves more than one-half of one side but not both sides
	T2c	Tumor involves both sides
	T3	Extraprostatic tumor that is not fixed or does not invade adjacent structures
	T3a	Extraprostatic extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
	T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
N – Regional Lymph Nodes	NX	Regional lymph nodes cannot be assessed
	N0	No positive regional nodes
	N1	Metastasis in regional lymph node(s)
M – Distant Metastasis	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Nonregional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s) with or without bone disease

8.2 Appendix 2

Table 15 – Characteristics of decay for most common radioactive isotopes used for BT treatments for localized prostate cancer.

Type of Dose-Rate	Radioactive Isotope	Half-life (days)	Principal Type of Decay	Mean Energy (MeV)
Low-Dose Rate	Iodine-125 (^{125}I)	60,1	ϵ	0,028
	Palladium-103 (^{103}Pd)	17	ϵ	0,021
	Cesium-131 (^{131}Cs)	9,7	ϵ	0,029

High-Dose Rate	Iridium-192 (^{192}Ir)	73,8	β^-	0,38
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8.3 Appendix 3

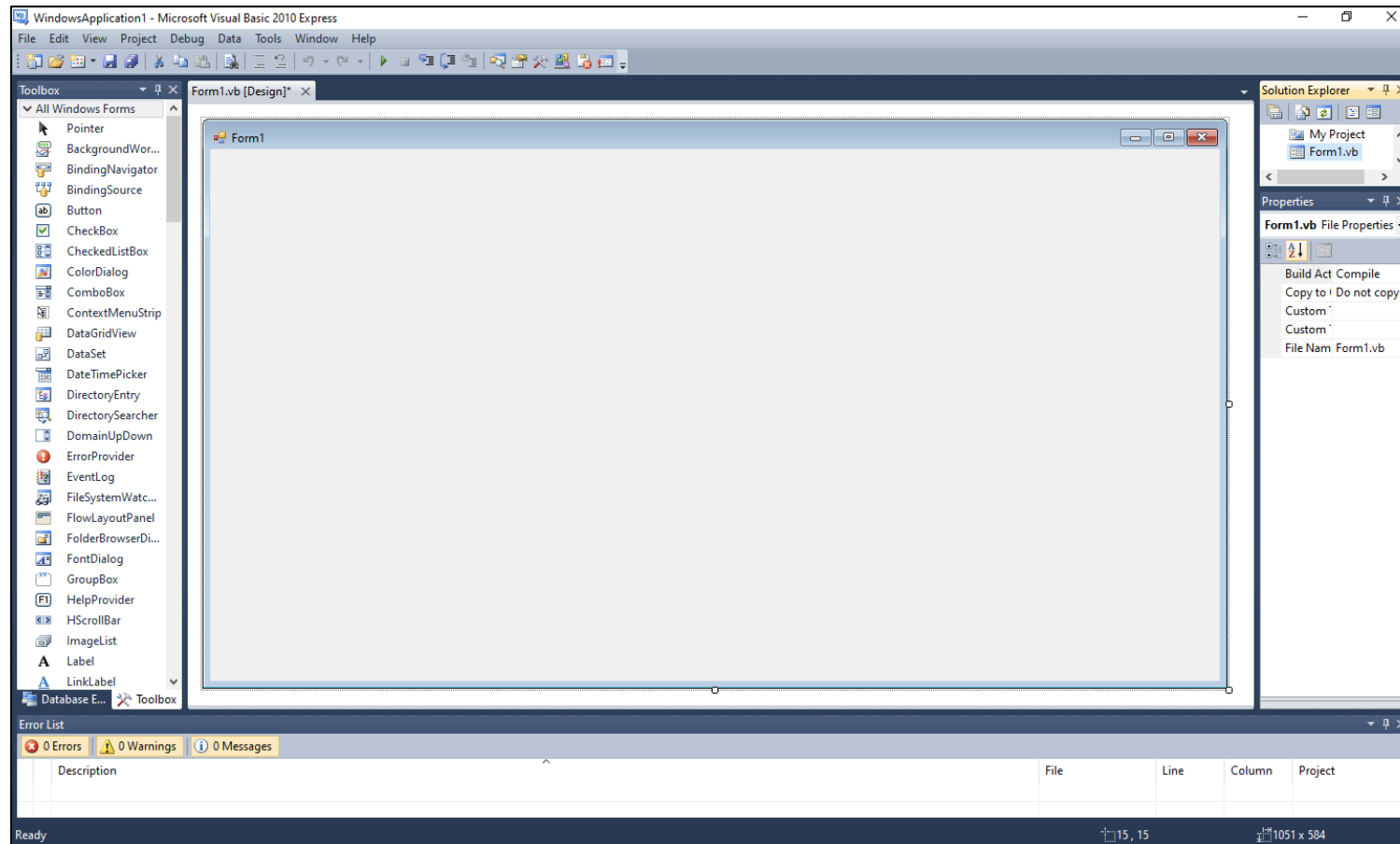


Figure 20 - Demonstration of a blank Windows form created with Visual Studio 2010 for the development of a Windows application using VB. On the center is represented the page in which user interface will be built. On the left are represented the available VB objects.

8.4 Appendix 4

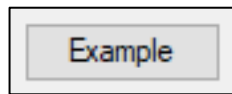


Figure 21 - Example of Button created using the toolbox from Visual Studio 2010.

8.5 Appendix 5

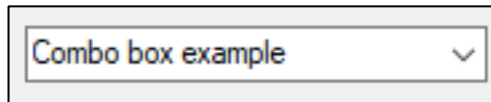


Figure 22 - Example of Combo box created using the toolbox from Visual Studio 2010.

8.6 Appendix 6

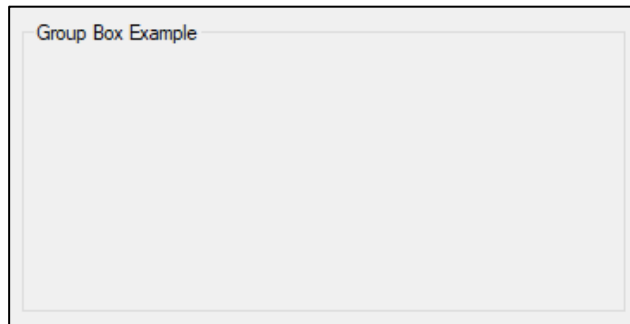


Figure 23 - Example of Group box created using the toolbox from Visual Studio 2010.

8.7 Appendix 7

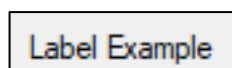


Figure 24 - Example of a Label created using the toolbox from Visual Studio 2010.

8.8 Appendix 8



Figure 25 - Example of a Link Label created using the toolbox from Visual Studio 2010.

8.9 Appendix 9



Figure 26 - Example of a Radio Button created using the tool box from Visual Studio 2010.

8.10 Appendix 10

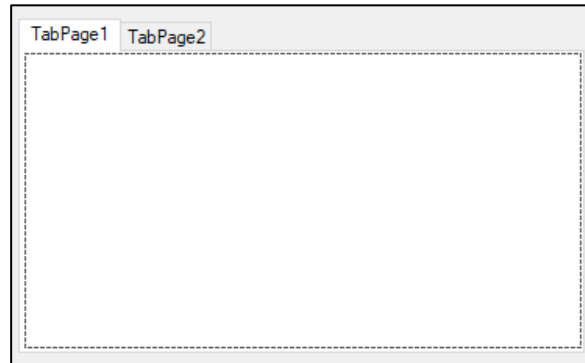


Figure 27 - Example of a Tab Control created using the toolbox from Visual Studio 2010.

8.11 Appendix 11



Figure 28 - Example of a Text box created using the tool box from Visual Studio 2010.

8.12 Appendix 12

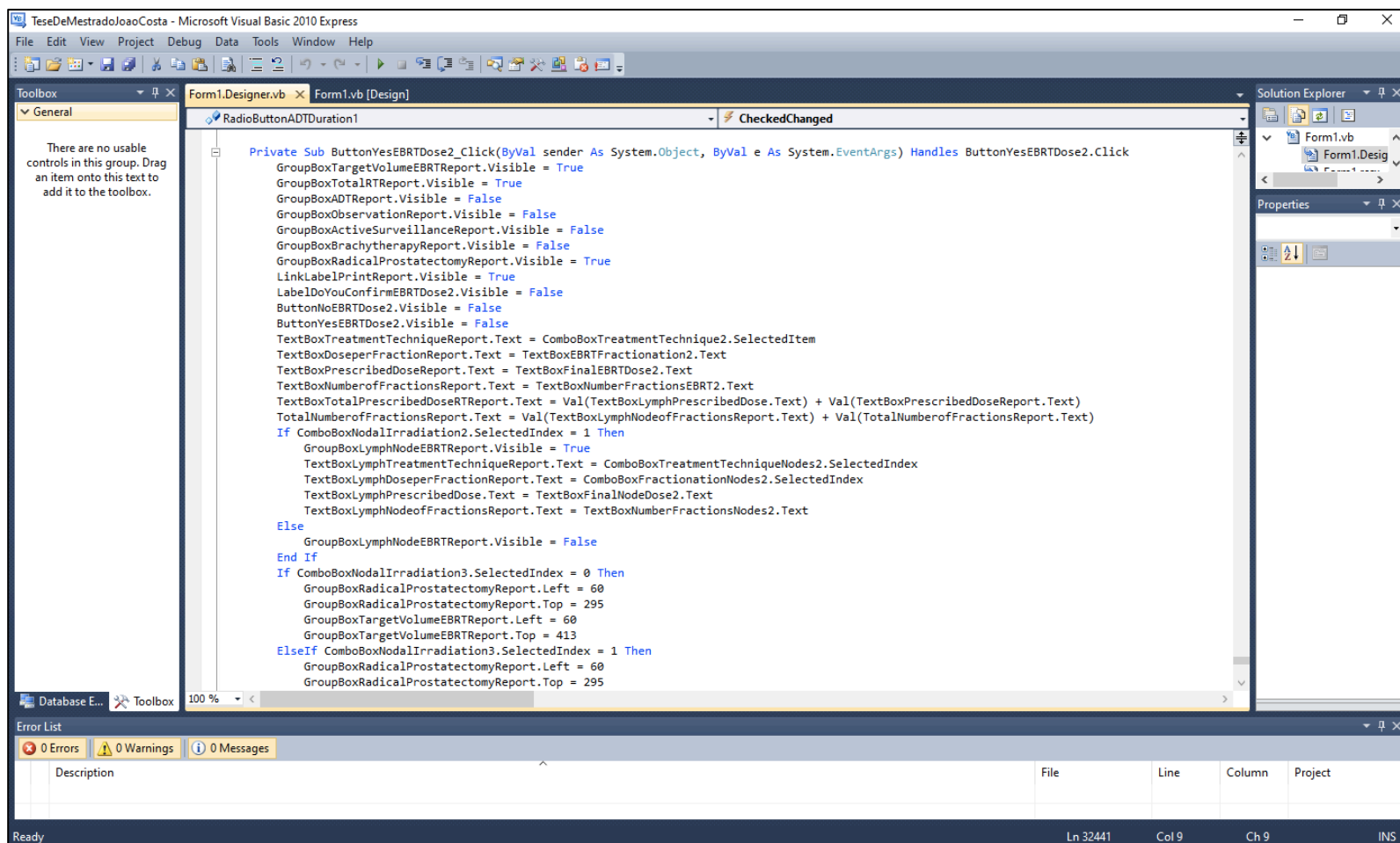


Figure 29 - Demonstration of the code page from Visual Studio 2010. The presented code is an if-then condition related to a button.

8.13 Appendix 13

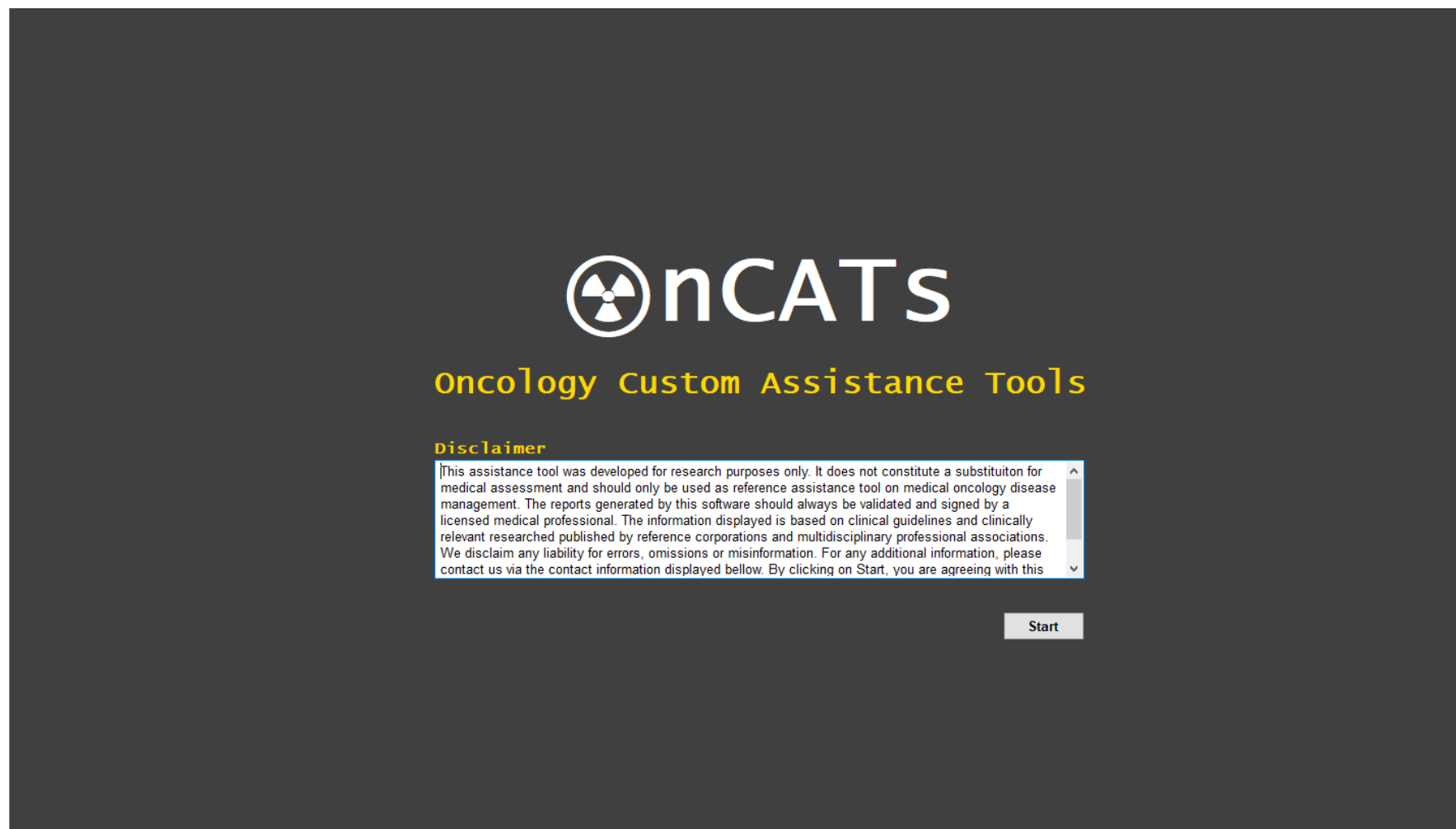


Figure 30 - Representation of the Home Page of the OnCATs DCSS.

8.14 Appendix 14

nCATs Treatment Access | Home [Risk Assessment](#) | Logged in as: admin

Patient Information

ID: 34243224324

Disease Site: Prostate

Risk Classification: Intermediate Risk

Treatment Course Assessment

Patient Life Expectancy: Calculate [v] years

Age: 55 years old (50 - 105)

Gleason Score: 7 Mortality Rate: 0.065

Lead Time: 10 years

Quartile of Health: Healthy (Middle 25-75%) [v]

Life Expectancy: 17.7 years

Death Risk of Prostate Cancer: 34.36 %

expectancy by adjusting the life expectancy from the Social S
the mortality rates associated with watchful waiting. The watch
are from a publication by Albertsen et. al (2005), which descr
diagnosed with prostate cancer before PSA came into use and
definitive local therapy. Researchers with access to mortality r
specify a custom mortality rate (deaths per 1000 person-year
mortality rate". The calculator also estimates the risk of dying
during the expected years of life.

Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative man
 prostate cancer. JAMA 2005;293:2095-2101.

Gleason score: Enter the overall Gleason score from the pro

Lead time: The mortality rates reported by Albertsen et. al (G
 patients diagnosed with prostate cancer before PSA came into
 to earlier detection of cancer, which is referred to as lead time
 detected as a result of PSA screening, and not as a result of c
 lead time should be included. It is estimated that PSA screenin
 approximately 10 years; however, there is no consensus amon

Figure 31 - Online life expectancy calculator for prostate cancer patients based on the methods of Kim et al.

8.15 Appendix 15

nCATs Prescription | Home Risk Assessment Treatment Access | Logged in as: [redacted]

Patient Information

ID: 232323 Treatment Course: EBRT

Disease Site: Prostate

Risk Classification: Intermediate Risk

Pelvic Lymph Node Irradiation ✓

Lymph Node Irradiation: Yes

Treatment Technique: Volumetric Modulated Arc Therapy (VMAT)

Dose Per Fraction: 2 Gy/Fraction **Calculate**

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

46 Gy 50 Gy 48 Gy

Target Volume External Beam Radiotherapy

Treatment Technique: Volumetric Modulated Arc Therapy (VMAT)

Fractionation: Moderate Hypofractionation

Dose Per Fraction: Other Gy/Fraction

Total Dose: Insert your desired Treatment Dose and Dose per Fraction.

60 Gy in fractions of 3 Gy/Fraction

Recommendations

Moderate Hypofractionation:

- No previous EBRT irradiation
- No previous malignancy in 5 years except localized basal or squamous skin cell carcinoma

References

Prophylactic Lymph Node Irradiation:
• (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54, 57–61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prescribed Dose to the Regional Lymph Nodes:

Aceda a Definições para ativar o Windows.

Figure 32 - Exemplification of OnCATs' tab for prescription of radical EBRT treatment.

8.16 Appendix 16

nCATs Prescription
Home Risk Assessment Treatment Access
Logged in as: admin

Patient Information

ID: Treatment Course: +

Disease Site:

Risk Classification:

Pelvic Lymph Node Irradiation ✓

Lymph Node Irradiation:

Treatment Technique:

Dose Per Fraction: Gy/Fraction

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

46 Gy 50 Gy

48 Gy

Target Volume External Beam Radiotherapy ✓

Treatment Technique:

Fractionation:

Dose Per Fraction: Gy/Fraction

Total Dose: Choose one of the following or click [here](#) to insert a new one.

72 Gy 78 Gy

74 Gy 80 Gy

76 Gy

Androgen Deprivation Therapy ✓

Type of ADT:

1st Line Approach:

ADT Duration: For surgical ADT options, the duration of the treatment is permanent

Permanent

Total Prescribed Dose

Gy on Gy per Fraction, in a total of Fractions prescribed to the Regional Lymph Nodes.

+

Gy on Gy per Fraction, in a total of Fractions prescribed to the Target Volume.

=

Gy + Androgen Deprivation Therapy

Do you confirm this information is correct?

References

Prescribed Dose to the Regional Lymph Nodes:

• Mottet N, Bergh R, CN van den, Briers E, Bourke L, Cornford P, Santis M De, et al. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer [Internet]. European Association of Urology 2018. 2018 [cited 2019 Dec 5]. p. 1–145. Available from: <https://uroweb.org/wp-content/uploads/EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-large-text-V2.pdf>

Figure 33 - Exemplification of OnCATs' tab for prescription of EBRT with ADT.

8.17 Appendix 17

nCATs Prescription | Home Risk Assessment Treatment Access | Logged in as: admin

Patient Information

ID: 1412414 Treatment Course: EBRT + BT

Disease Site: Prostate

Risk Classification: Intermediate Risk

Pelvic Lymph Node Irradiation ✓

Treatment Technique: 3D Conformal Radiotherapy (3DCRT)

Dose Per Fraction: 2

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

46 Gy 50 Gy 48 Gy

Brachytherapy Boost ✓

Dose Rate: High Dose Rate (HDR)

Radioactive Isotope: Iridium-192

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

12 Gy, delivered in 1 fraction(s)

15 Gy, delivered in 1 fraction(s)

21,5 Gy, delivered in 2 fraction(s)

Total Prescribed Dose

37,5 Gy on 2,5 Gy per Fraction, in a total of 15 Fractions prescribed to the Regional Lymph Nodes.

+ 15 Gy on 15 Gy per Fraction, in a total of 1 Fractions prescribed to the Target Volume.

= 52,5 Gy

Do you confirm this information is correct?

References

Prophylactic Lymph Node Irradiation:
• (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prescribed Dose to the Regional Lymph Nodes:

Figure 34 - Exemplification of OnCATs' tab for prescription of EBRT with adjuvant BT.

8.18 Appendix 18

nCATs Prescription
Home Risk Assessment Treatment Access
Logged in as: admin

Patient Information

ID: Treatment Course: + +

Disease Site:

Risk Classification:

Pelvic Lymph Node Irradiation ✓

Treatment Technique:

Dose Per Fraction:

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

46 Gy 50 Gy 48 Gy

Brachytherapy Boost ✓

Dose Rate:

Radioactive Isotope:

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

12 Gy, delivered in fraction(s)

15 Gy, delivered in fraction(s)

21,5 Gy, delivered in fraction(s)

Androgen Deprivation Therapy ✓

Type of ADT:

1st Line Approach:

ADT Duration: Choose one of the following or click here to insert a new one.

4 Months

Total Prescribed Dose

Gy on Gy per Fraction, in a total of Fractions prescribed to the Regional Lymph Nodes.

+

Gy on Gy per Fraction, in a total of Fractions prescribed to the Target Volume.

=

Gy + Months of Androgen Deprivation Therapy

Do you confirm this information is correct?

References

Prophylactic Lymph Node Irradiation:
 • (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prescribed Dose to the Regional Lymph Nodes:

Figure 35 - Exemplification of OnCATs' tab for prescription of EBRT with adjuvant BT and ADT.

8.19 Appendix 19

nCATs Prescription | Home | Risk Assessment | Treatment Access | Logged in as: admin

Patient Information

ID: 96875856 Treatment Course: RP + PLND + ADT

Disease Site: Prostate

Risk Classification: High Risk

Radical Prostatectomy and Pelvic Lymph Node Dissection

The procedure will be performed by a retropubic approach in order to remove the whole prostate gland with a single incision. The patient will be positioned on prone position on the surgical table, under general anesthesia. An extended PLND should be performed at the same time, using the following limits anterior: external iliac vein, lateral: pelvic sidewall, medial: bladder wall; posterior: floor of the pelvis; distal: cooper's ligament and proximal: internal iliac vein.

Androgen Deprivation Therapy

Type of ADT: LHR Agonist + Non-Steroidal Antiandrogen

1st Line Approach: Goserelin Flutamide

ADT Duration: Choose one of the following or click [here](#) to insert a new one.

6 Months

Do you confirm this information is correct? No Yes

References

- (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57–61, 65–75, 96–. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
- Committee National Clinical Effectiveness. Diagnosis, staging and treatment of patients with prostate cancer National Clinical Effectiveness Committee [Internet]. 2015 [cited 2019 Dec 5]. Available from: <http://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/prostateguideline.pdf>

Figure 36 - Exemplification of OnCATs' tab for prescription of RP with PLND and adjuvant ADT.

8.20 Appendix 20

nCATs Prescription
Home Risk Assessment Treatment Access
Logged in as: admin

Patient Information

ID: Treatment Course: +

Disease Site:

Risk Classification:

Radical Prostatectomy Description ✓

The procedure will consist on the removal of the whole prostate gland using a retropubic approach. The patient will be positioned on supine position on the surgical table. The procedure will be performed with the patient under general anesthesia.

Prostate Bed External Beam Radiotherapy ✓

Treatment Technique:

Fractionation:

Dose Per Fraction: Gy/Fraction

Total Dose: Choose one of the following or click [here](#) to insert a new one.

64 Gy 70 Gy

66 Gy 72 Gy

68 Gy

Lymph Node Irradiation ✓

Lymph Node Irradiation:

Treatment Technique:

Dose Per Fraction: Gy/Fraction

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

46 Gy 50 Gy

48 Gy

Total Prescribed Dose

Gy on Gy per Fraction, in a total of Fractions prescribed to the Regional Lymph Nodes.

+

Gy on Gy per Fraction, in a total of Fractions prescribed to the Target Volume.

=

Gy

Do you confirm this information is correct?

References

Prescribed Dose to the Prostate Bed:
 • (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Prescribed Dose to the Regional Lymph Nodes:
 • Mottet N, Bergh R. CN van den, Briers E, Bourke L, Cornford P, Santis M De, et al. EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer [Internet]. European Association of Urology 2018. 2018 [cited 2019 Dec 5]. p. 1–145. Available from: <https://uroweb.org/wp->

Figure 37 - Exemplification of OnCATs' tab for prescription of RP with adjuvant EBRT.

8.21 Appendix 21

nCATs Prescription
Home Risk Assessment Treatment Access
Logged in as: admin

Patient Information

ID: Treatment Course: + +

Disease Site:

Risk Classification:

Radical Prostatectomy Description ✓

The procedure will be performed under general anesthesia with the patient positioned on the surgical table in supine position. A retropubic approach will be used in order to remove the whole prostate gland.

Prostate Bed External Beam Radiotherapy ✓

Treatment Technique:

Fractionation:

Dose Per Fraction: Gy/Fraction

Total Dose: Choose one of the following or click [here](#) to insert a new one.

Gy Gy

Gy Gy

Gy

Lymph Node Irradiation ✓

Lymph Node Irradiation:

Treatment Technique:

Dose Per Fraction: Gy/Fraction

Treatment Dose: Choose one of the following or click [here](#) to insert a new one.

Gy Gy

Gy

Total Prescribed Dose

Gy on Gy per Fraction, in a total of Fractions prescribed to the Pelvic Lymph Nodes.

+

Gy on Gy per Fraction, in a total of Fractions prescribed to the Target Volume.

=

Gy + Months of Androgen Deprivation Therapy

Androgen Deprivation Therapy ✓

Type of ADT:

1st Line Approach:

Do you confirm this information is correct?

References

Prescribed Dose to the Prostate Bed:
 • (NCCN®) Nacional Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

Figure 38 - Exemplification of OnCATs' tab for prescription of RP with adjuvant EBRT and ADT.

8.22 Appendix 22

nCATs Prescription
Home Risk Assessment Treatment Access | Logged in as: admin

Patient Information

ID: Treatment Course: + +

Disease Site:

Risk Classification:

Radical Prostatectomy and Pelvic Lymph Node Dissection Description ✓

The procedure will be performed by a retropubic approach in order to remove the whole prostate gland with a single incision. The patient will be positioned on prone position on the surgical table, under general anesthesia. An extended PLND should be performed at the same time, using the following limits anterior: external iliac vein, lateral: pelvic sidewall, medial: bladder wall; posterior: floor of the pelvis; distal: cooper's ligament and proximal: internal iliac vein.

Observation Protocol

PSA Blood Test: Performed at day 1 and then every months.

Digital Rectal Exam: Performed at day 1 and then every months.

Protocol Duration:

Adjuvant Treatment(s):

Do you confirm this information is correct?

References

Radical Prostatectomy and Pelvic Lymph Node Dissection Description:

- Radical Prostatectomy description defined by criteria defined by the user admin on 08/01/2020.

Observation Protocol

- (NCCN®) National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Prostate Cancer [Internet]. NCCN Guidelines for Patients®. 2019 [cited 2019 Jun 1]. p. 11–9, 22, 34–7, 47, 50, 51, 54,57-61, 65–75, 96-. Available from: [\[link\]](#)

Figure 39 - Exemplification of OnCATs' tab for prescription of RP with adjuvant Observation.

9. Annexes

9.1 Annex 1

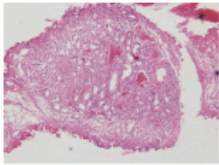
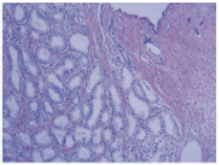
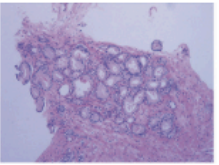
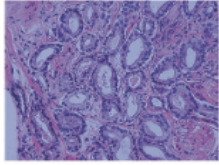
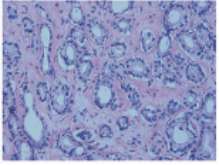
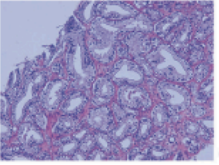
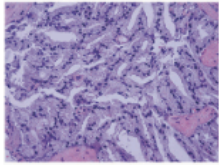
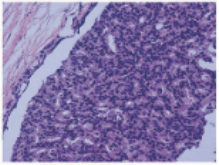
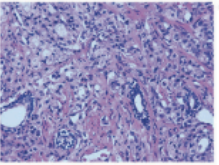
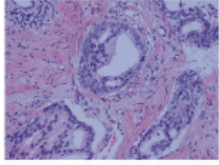
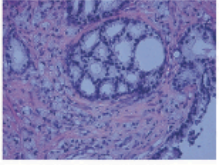
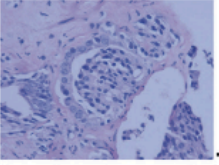
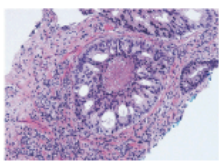
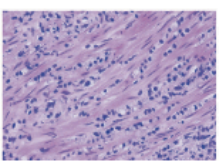
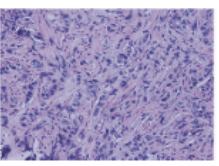
			Gleason patterns 1–3 distinct, discrete, individual glands	Gleason score ≤ 6	Grade group I		
						Gleason score $3+4=7$	Grade group II
						Gleason score $4+3=7$	Grade group III
			Gleason pattern 4 fused, cribriform, or poorly-formed glands, or glomerular	Gleason score $4+4=8$ $3+5=8$ $5+3=8$	Grade group IV		
				Gleason score $4+5=9$ $5+4=9$ $5+5=10$	Grade group V		
				Gleason pattern 5 comedo necrosis, cords, sheets, solid nests, single cells			

Figure 40 - Representation of the GS grading system with histologic images of the different patterns on a cellular level.

9.2 Annex 2

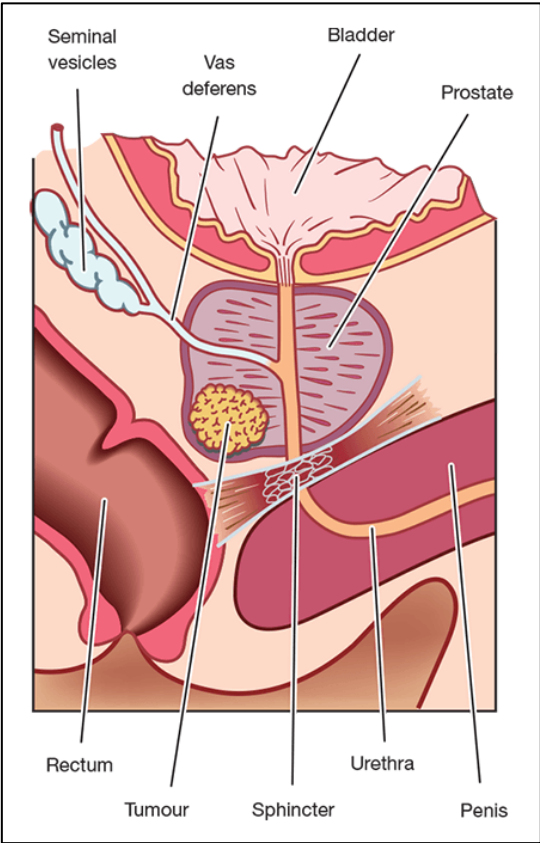


Figure 41 - Representation of the genitourinary anatomy of a healthy male.

9.3 Annex 3

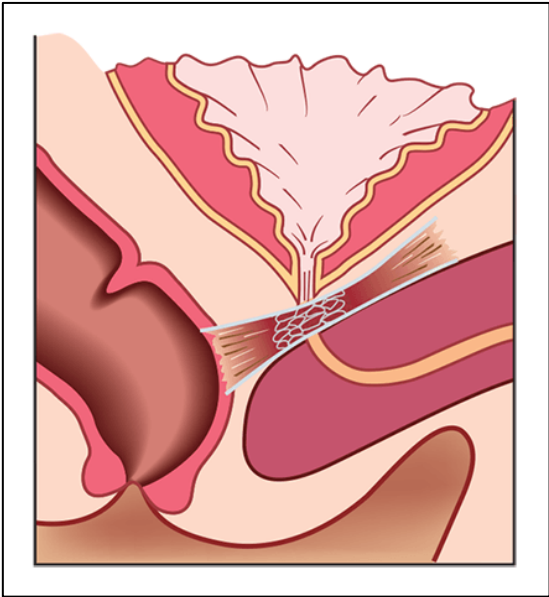


Figure 42 - Representation of the genitourinary anatomy of a human male after being submitted to a RP.

9.4 Annex 4

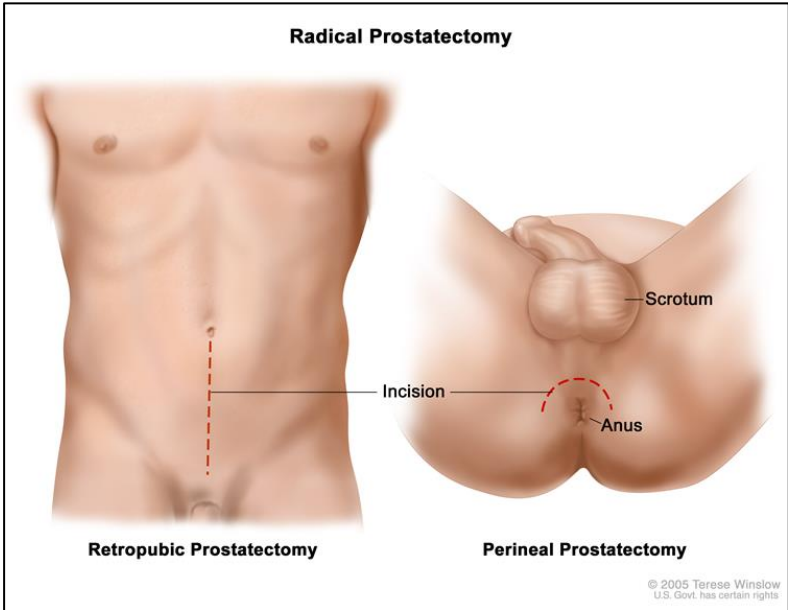


Figure 43 - Representation of a retropubic incision and a perineal incision for performing a RP surgery.

9.5 Annex 5

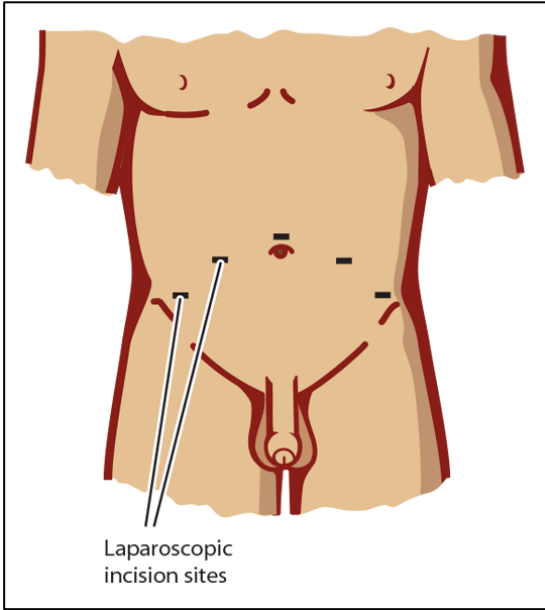


Figure 44 - Representation of an example of the surgical incisions performed on a laparoscopic RP.

9.6 Annex 6

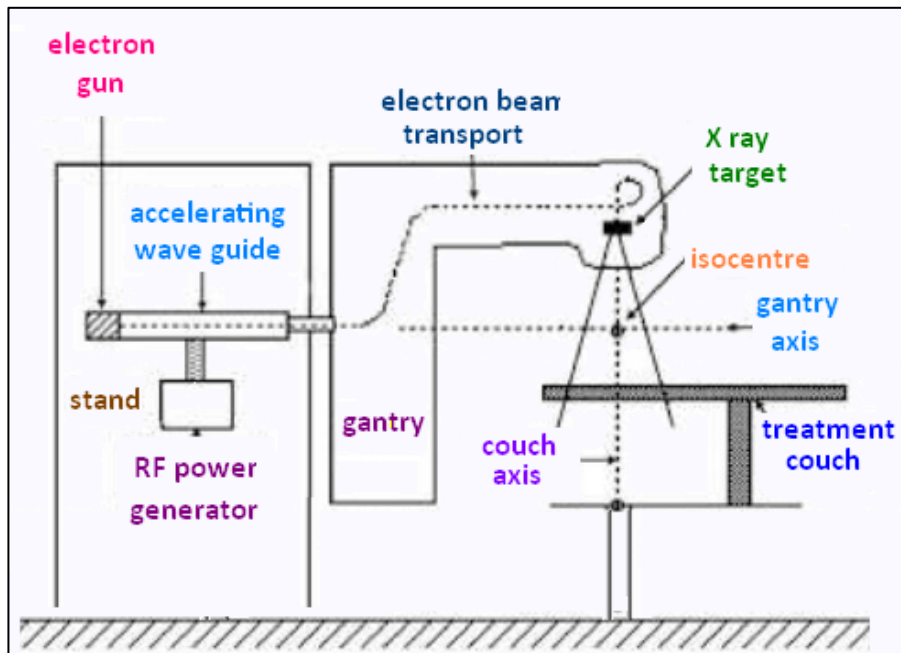


Figure 45 - Visual representation of a conventional linac used for EBRT treatments and its components.

9.7 Annex 7

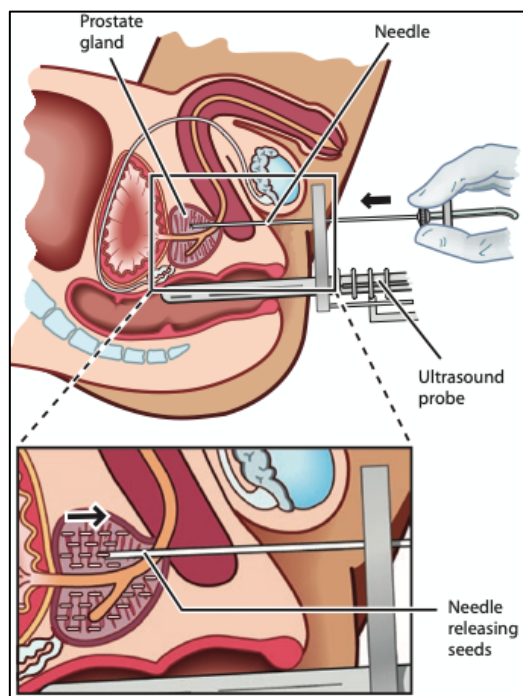


Figure 46 - Visual representation of an ultra-sound guided procedure of source placement for LDR BT treatments.

9.8 Annex 8

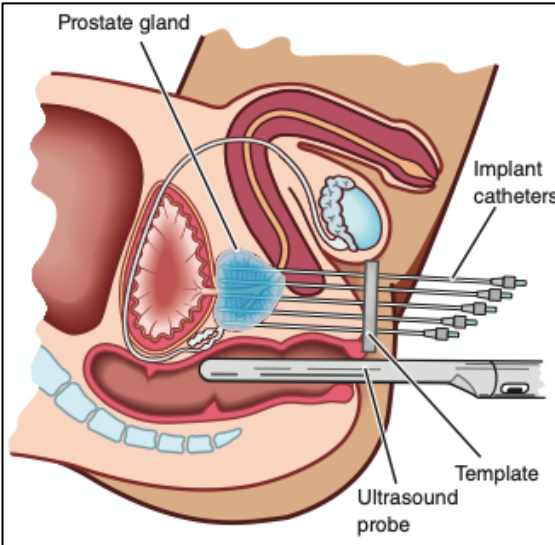


Figure 47 - Visual representation of an ultra-sound guided procedure of source placement for HDR BT treatments.

9.9 Annex 9

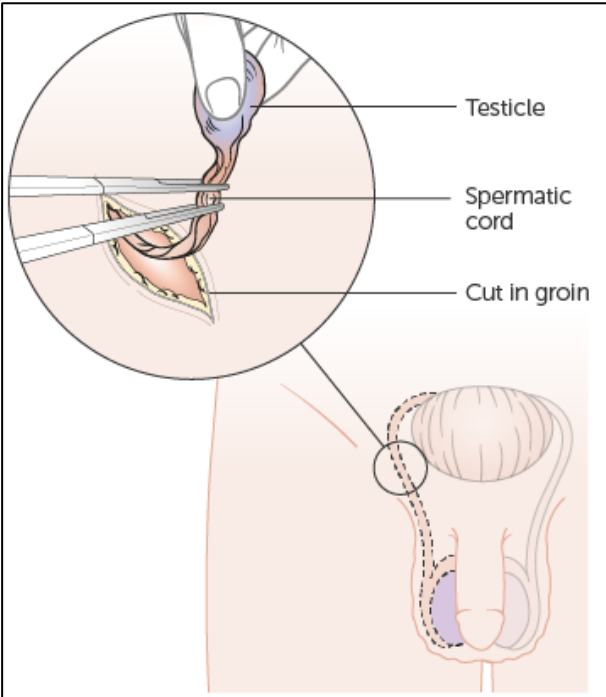


Figure 48 - Visual representation of a surgical orchidectomy.